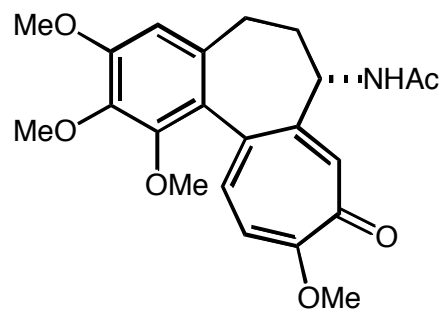
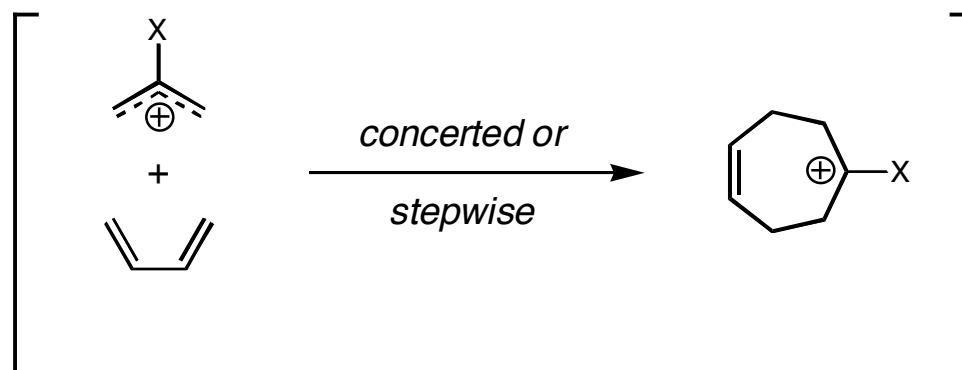
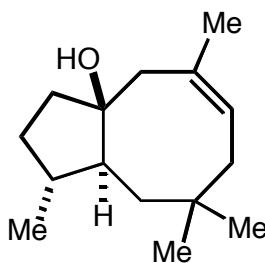


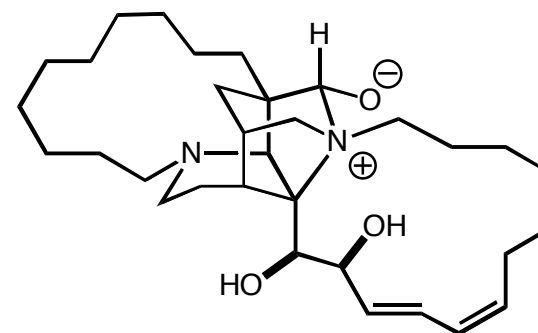
[4+3] Cycloadditions and Their Application in Synthesis



Colchicine



Dactyol



Sarain A

An Evans Group Friday Afternoon Seminar

February 4th, 2004

Jonathan F. Lawrence

Contents:

- Reactivity of (oxy)allyl cations
- Mechanism of [4+3] cycloadditions
- Intermolecular reactions
- Intramolecular reactions
- Asymmetric reactions
- Miscellaneous uses in complex synthesis

Review articles:

H.M.R. Hoffmann:

"Synthesis of Seven- and Five-Membered Rings from Allyl Cations", *ACIEE*, 12, 819 (1973).

"The Cycloaddition of Allyl Cations to 1,3-Dienes", *ACIEE*, 23, 1 (1984).

"8-Oxabicyclo[3.2.1]oct-6-en-3-ones: application to the Asymmetric Synthesis of Polyoxygenated Building Blocks", *ACIEE*, 43, 1934 (2004).

"The Synthetic Utility of Oxyallyl Cations", John Mann, *Tetrahedron*, 42, 4611 (1986).

W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Ch.4, Pergamon Press, 1990.

A. Hosomi and Y. Tominaga, "[4+3] Cycloaddition Reactions", *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 593.

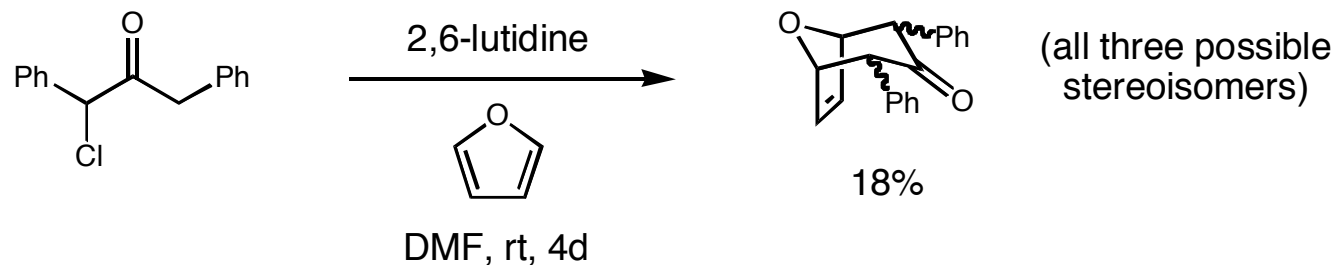
J. Rigby and F. Pigge, "[4+3] Cycloaddition Reactions", *Organic Reactions*, Paquette, L.A. et al, Eds.; Wiley & Sons: 1997; Vol. 51, p. 351.

"Intramolecular Cycloaddition Reactions of Allylic Cations", Michael Harmata, *Tetrahedron*, 53, 6235 (1997).

"Cycloaddition Reactions of Vinyl Oxocarbenium Ions", Michael Harmata, *Tetrahedron*, 59, 2371 (2003).

First Report

Fort, 1962:



Fort, *JACS*, 1962, 84, 4979.

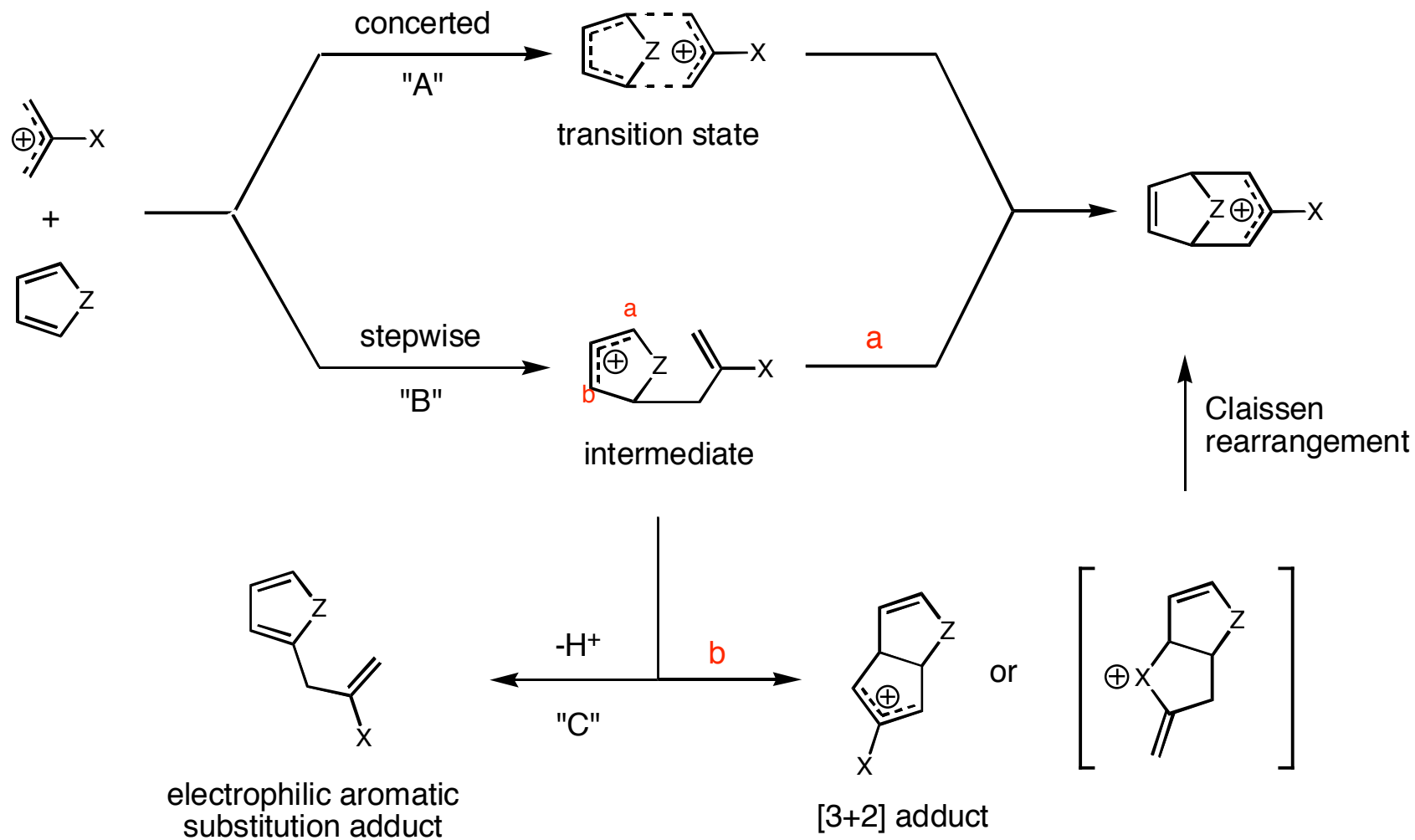
Cookson, 1963-1967:

Cookson subsequently improved the yield of cycloadducts by modifying the conditions:

<u>conditions</u>	<u>yield</u>
alkaline alumina in furan	40%
Zn/Cu couple	29%
Hg	35%
NaI in furan	quant.

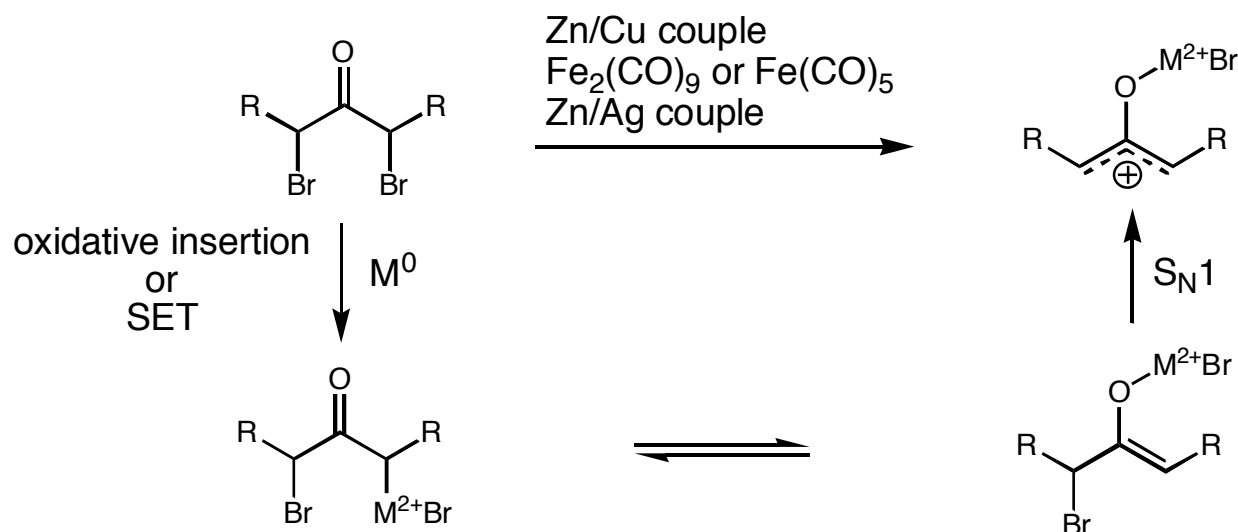
Cookson, *Proc.Chem.Soc.London*, 1963, 129.
J.Chem.Soc., 1965, 2009.
J.Chem.Soc. B., 1967, 473.

Mechanism of [4+3] Cycloadditions



Methods of Generating Allyl Cations I

Early work focused on reductive dehalogenation of polyhalo ketones with low valent metals:

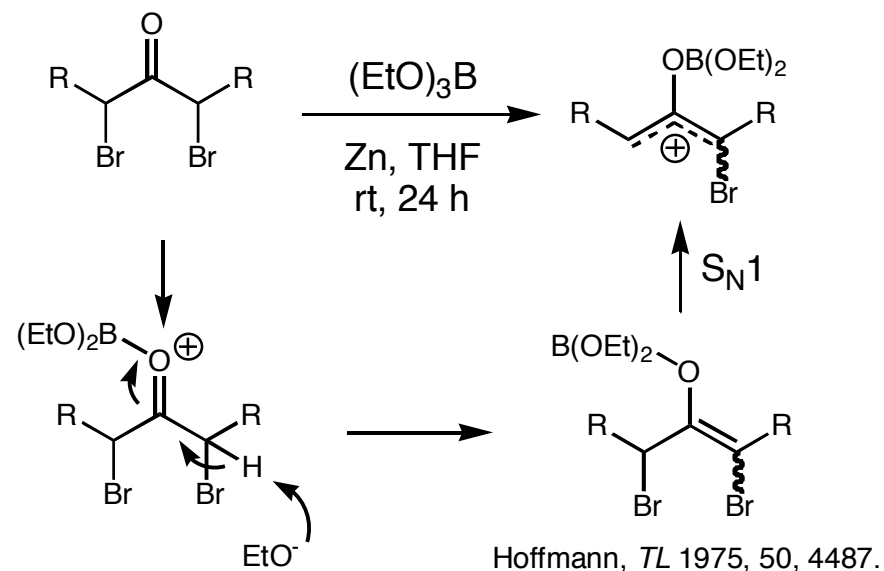
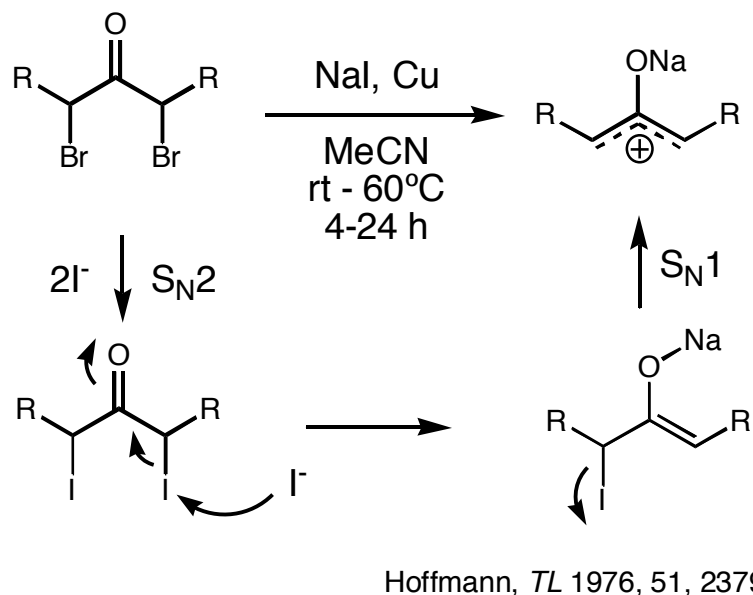


Zn/Cu: Hoffmann, *JACS* 1972, 94, 3940.

Fe: Noyori, *JOC* 1975, 40, 2681.

Zn/Ag: Noyori, *Bull.Chem.Soc.Jpn.*, 1978, 51, 2745.

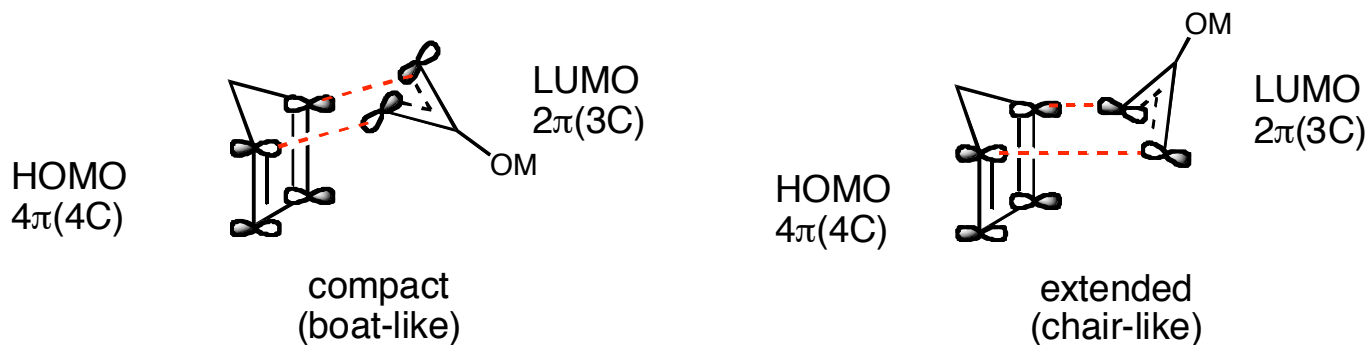
Other methods used with polybromoketones:



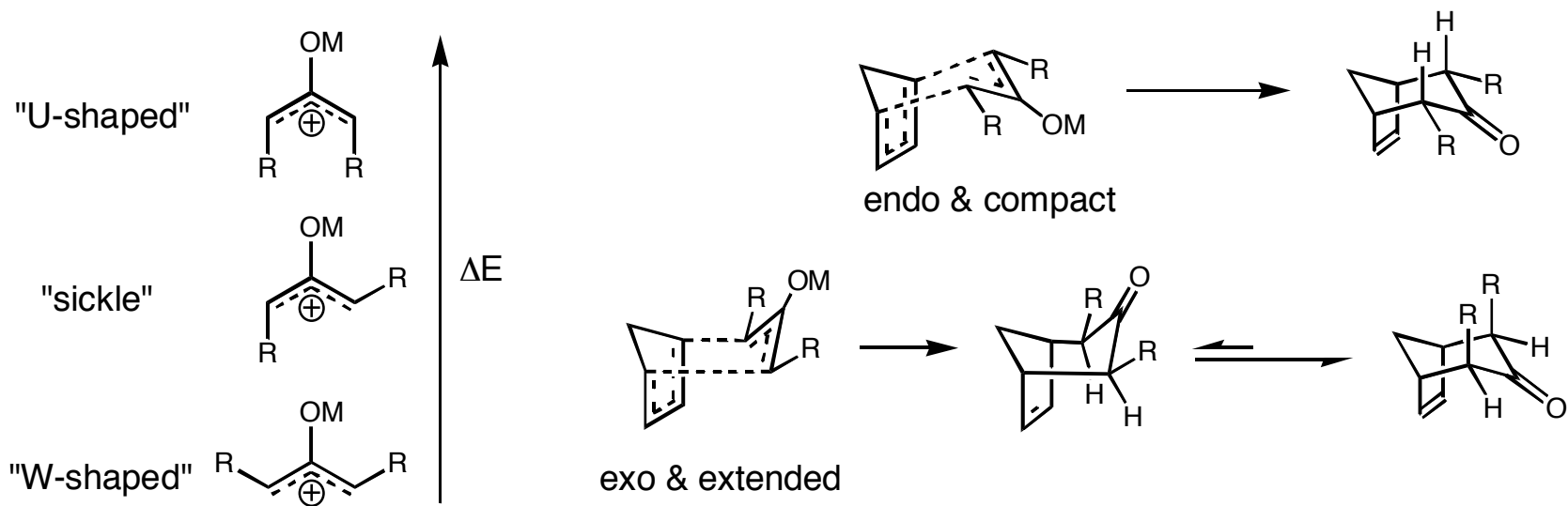
Transition State Analysis

Stereoselectivity of a [4+3] reaction is more complex than its lower [4+2] homolog:

There are two topologically distinct transition states:

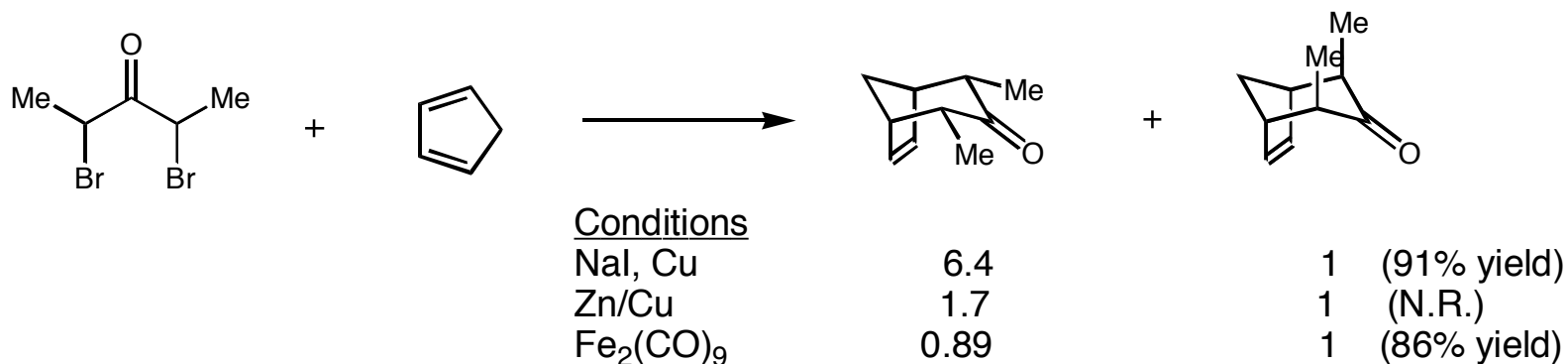


The cation can adopt three different configurations, which further complicates stereochemical analysis

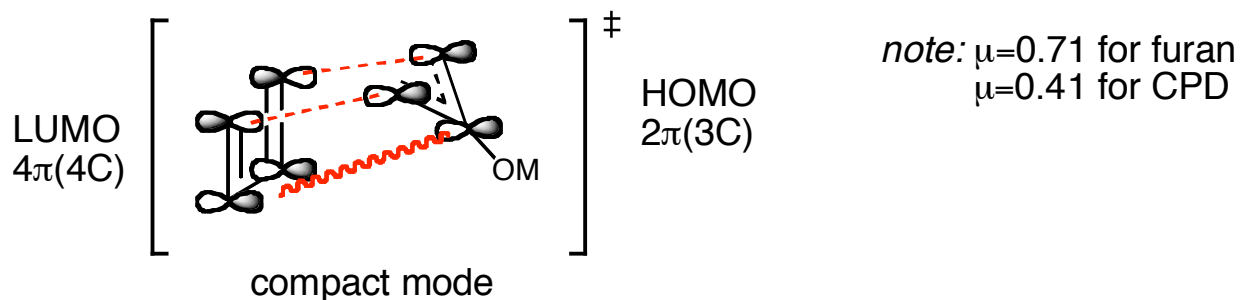


Stereoselectivity of Oxallyl Cations

The electrophilicity of the oxallyl cation determines transition state topology



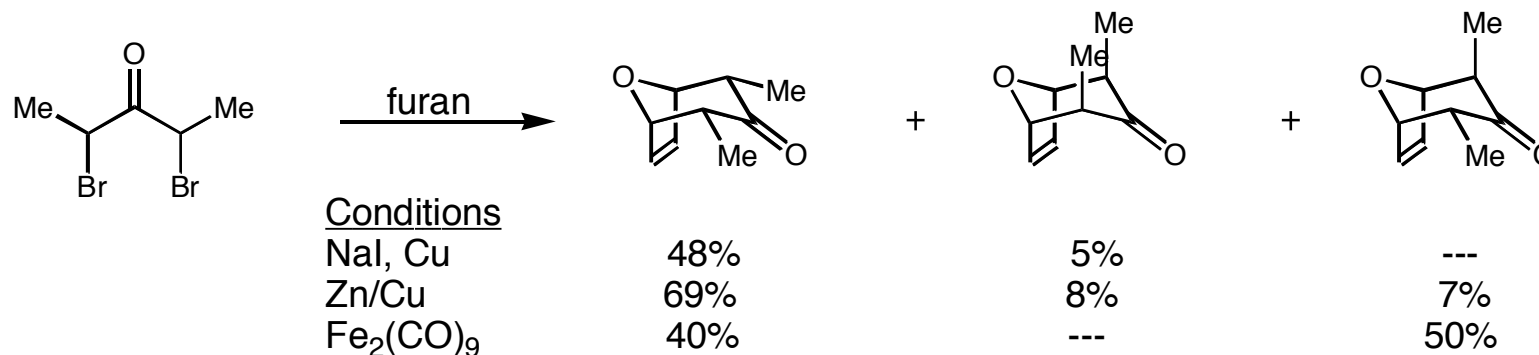
- More covalent oxygen-metal bonds give more stable and electrophilic oxallyl cations
- factors determining extended/compact modes:
 - dipole minimization favors compact mode for more highly charged oxygen
 - larger steric environment around the metal center favors extended mode
 - destabilizing secondary orbital interactions favor extended mode for unstable oxallyl cations



- In general, greater electrophilicity of the allyl cation favors an extended transition state

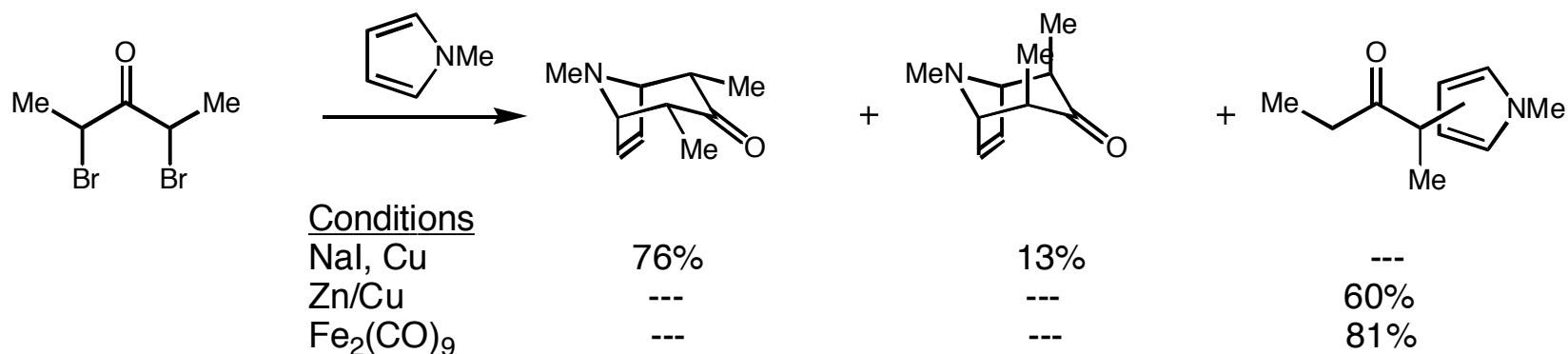
Stereoselectivity of Oxyallyl Cations II

Product distribution implicates a concerted or stepwise mechanism



- oxyallyl cations are assumed to have a "W" conformation, therefore:
 - di-axial and di-equatorial products are assumed to arise *via* a concerted mechanism
 - axial-equatorial product is assumed to arise *via* a stepwise mechanism
- More electrophilic cations (i.e. iron conditions) give access to a stepwise cycloaddition due to a greater mismatch in reactivity with dienes (*think hard-soft interactions!*)

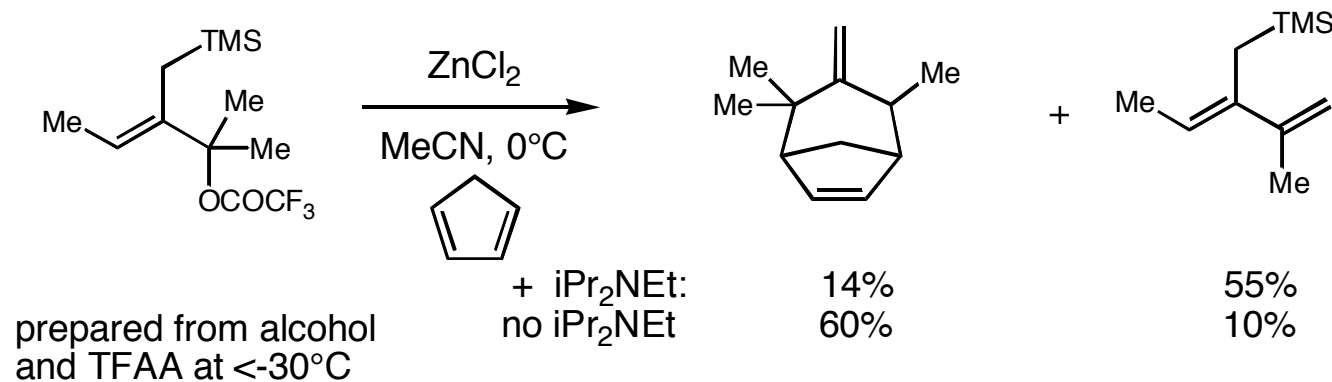
This is emphasized in the following reactions with the nucleophilic pyrrole:



- [4+3] products arise from Zn/Cu and Fe₂(CO)₉ conditions by using *N*-acyl and *N*-carboalkoxy-pyrroles to temper the reactivity of the diene component.

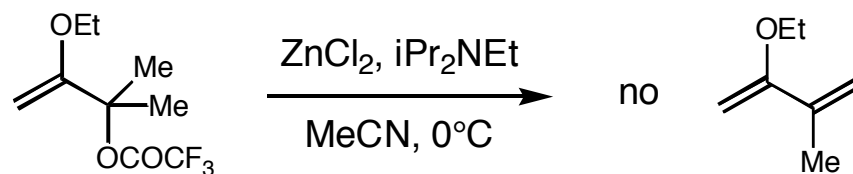
Reactivity of Allyl Cations

Oxyallyl cations do not eliminate (E1) readily:



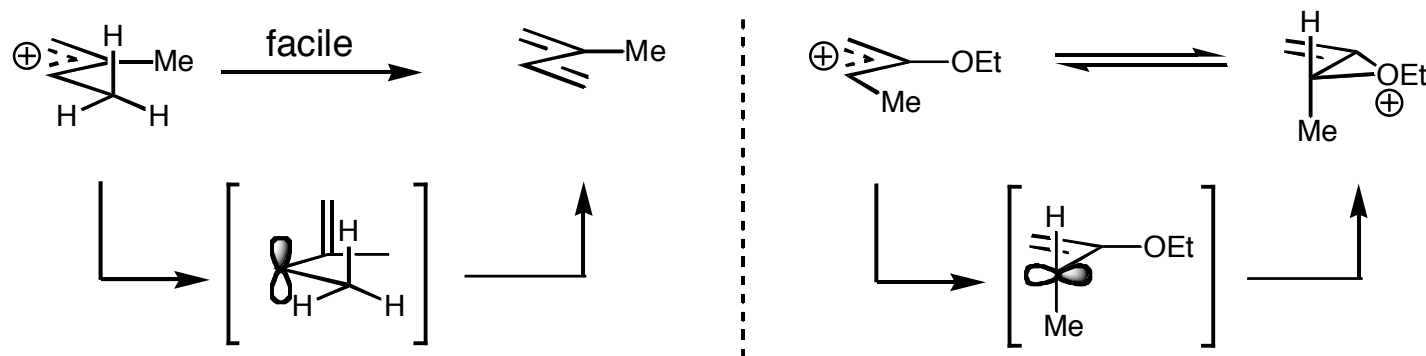
Hoffmann, *TL* 1982, 23, 2305.

however:



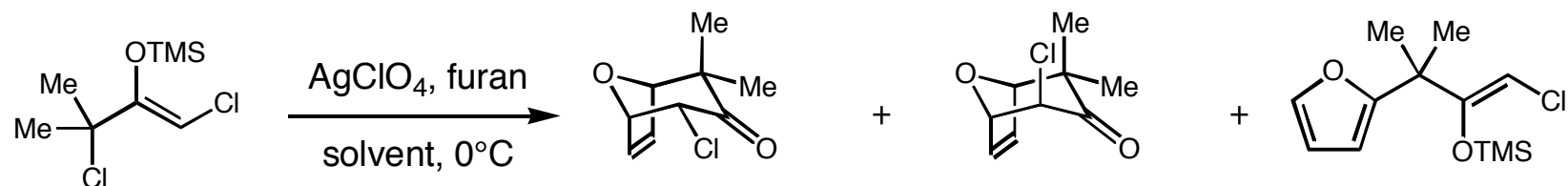
Hoffmann, *Chem. Ber.* 1980, 113, 3837.

because:



Reactivity of Allyl Cations II

Solvent can have an effect on the mechanism of reaction:



Solvent

MeNO₂

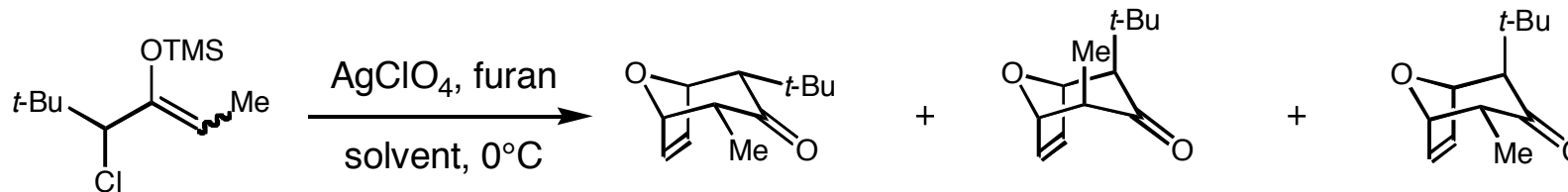
THF/Et₂O (1:1-3)

89%

2.6%

0.4%

61%



Solvent

MeNO₂

THF/Et₂O (1:1-3)

63%

16%

37%

22%

10%

- The authors suggest that a concerted cycloaddition takes place in MeNO₂ while a stepwise mechanism operates in THF/Et₂O
- Hoffmann: "A reaction of a structurally defined cation belongs at most to two classes, *i.e.* classes A and B or classes B and C. Thus, formation of class C products precludes class A as a source of cycloaddition and conversely, operation of a class A reaction makes it unlikely that products of class C are formed."

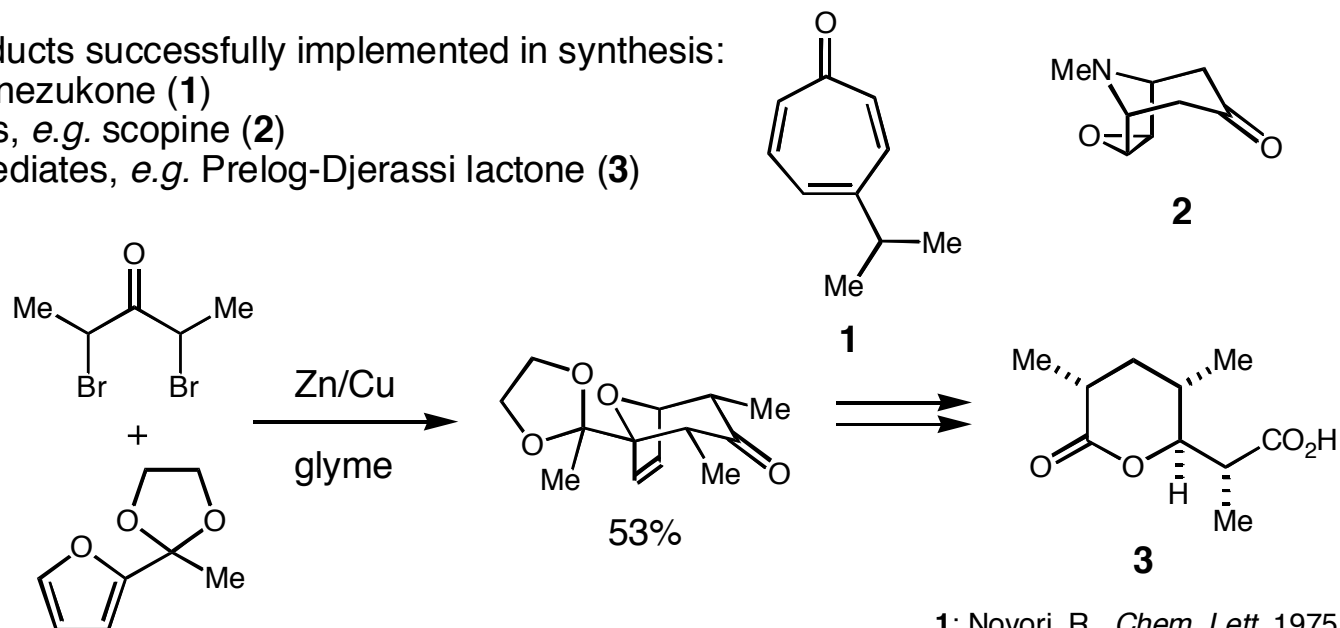
Early Uses of [4+3] Cycloadditions in Synthesis

Examples of [4+3] adducts successfully implemented in synthesis:

tropans, *e.g.* nezukone (1)

tropane alkaloids, *e.g.* scopine (2)

synthetic intermediates, *e.g.* Prelog-Djerassi lactone (3)

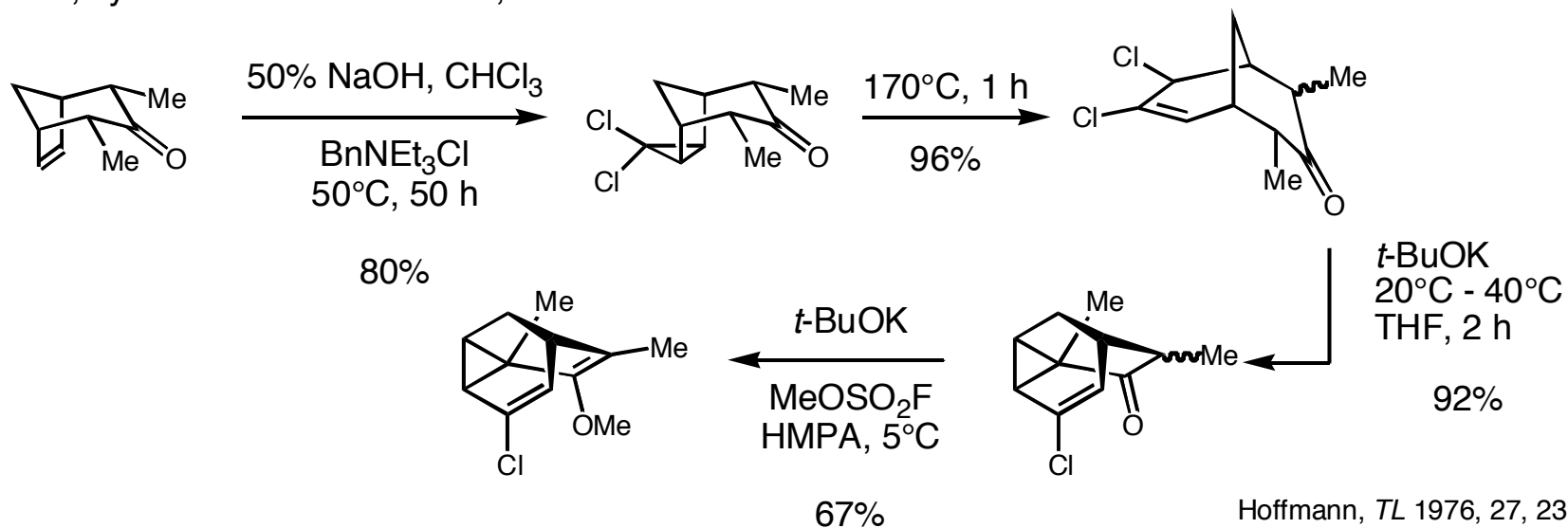


1: Noyori, R., *Chem. Lett.* 1975, 509.

2: Noyori, R., *JACS* 1974, 96, 3336.

3: White, J.D., *JACS* 1979, 101, 226.

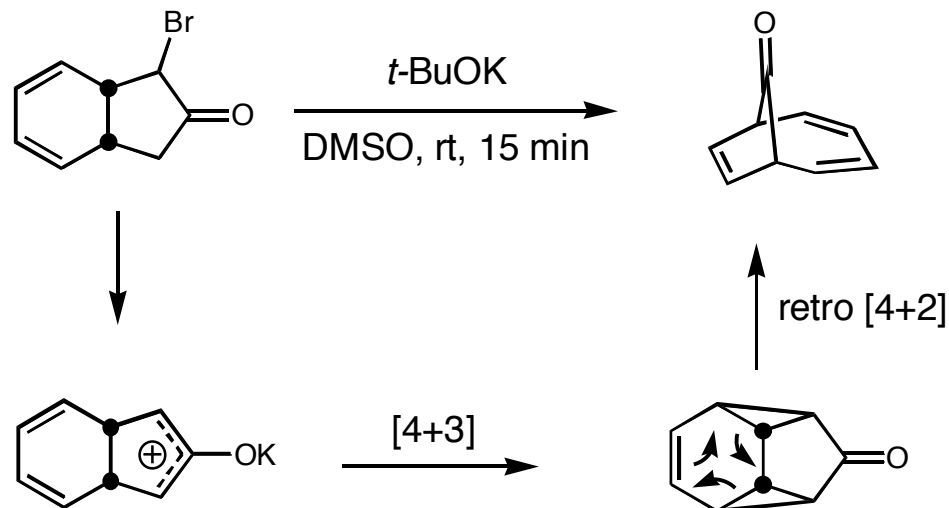
Hoffmann, synthesis of Barbaralanes, 1976:



Hoffmann, *TL* 1976, 27, 2382.

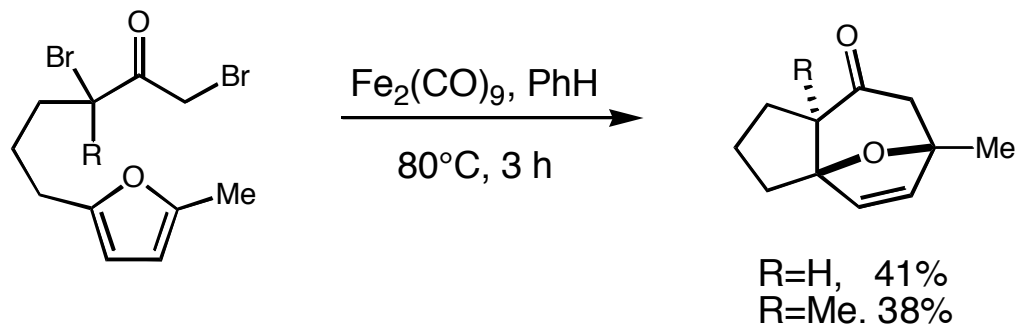
Early Uses of Intramolecular [4+3] Cycloadditions

An interesting purported intramolecular [4+3] cycloaddition:



Paquette, L.A. *JACS* 1973, 95, 2230.

The first intramolecular [4+3] cycloaddition:



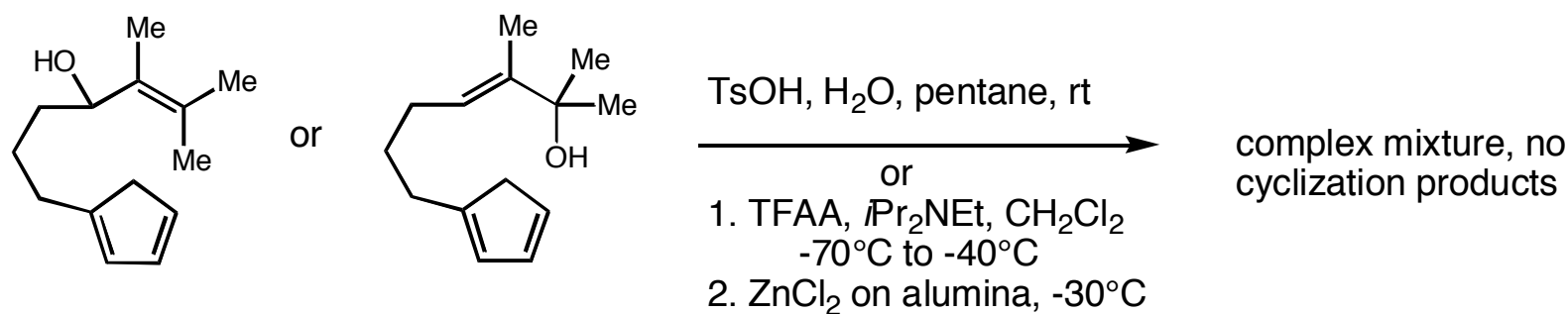
- Only example using these conditions, due to difficulty in obtaining starting ketone

Noyori, R., *JACS* 1979, 101, 220.

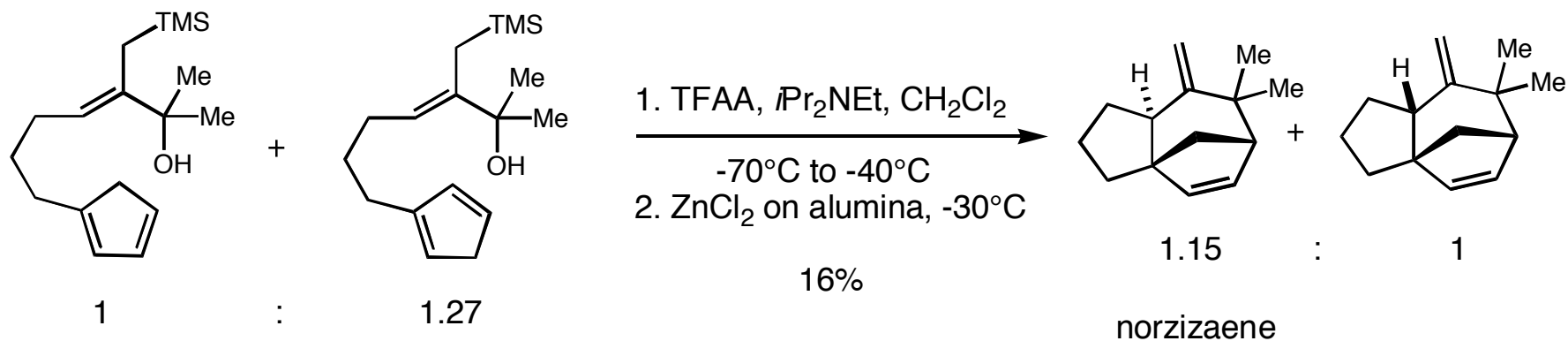
Intramolecular [4+3] Cycloadditions

- Intramolecular [4+3] cycloadditions have a control element not available to the intermolecular variant, so highly stereoselective reactions less dependent on the reaction conditions are possible.
- Products of intramolecular reactions are complex carbocyclic architectures

Early intramolecular examples show that selectivity is as highly dependent on conditions and substrate as the intermolecular reactions previously described:

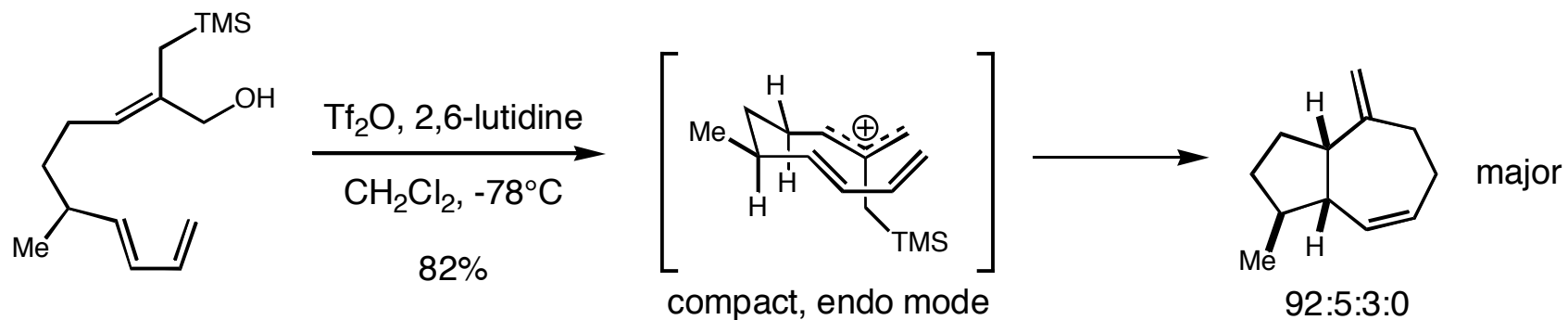


- these conditions led to [4+3] adducts in the intermolecular cases

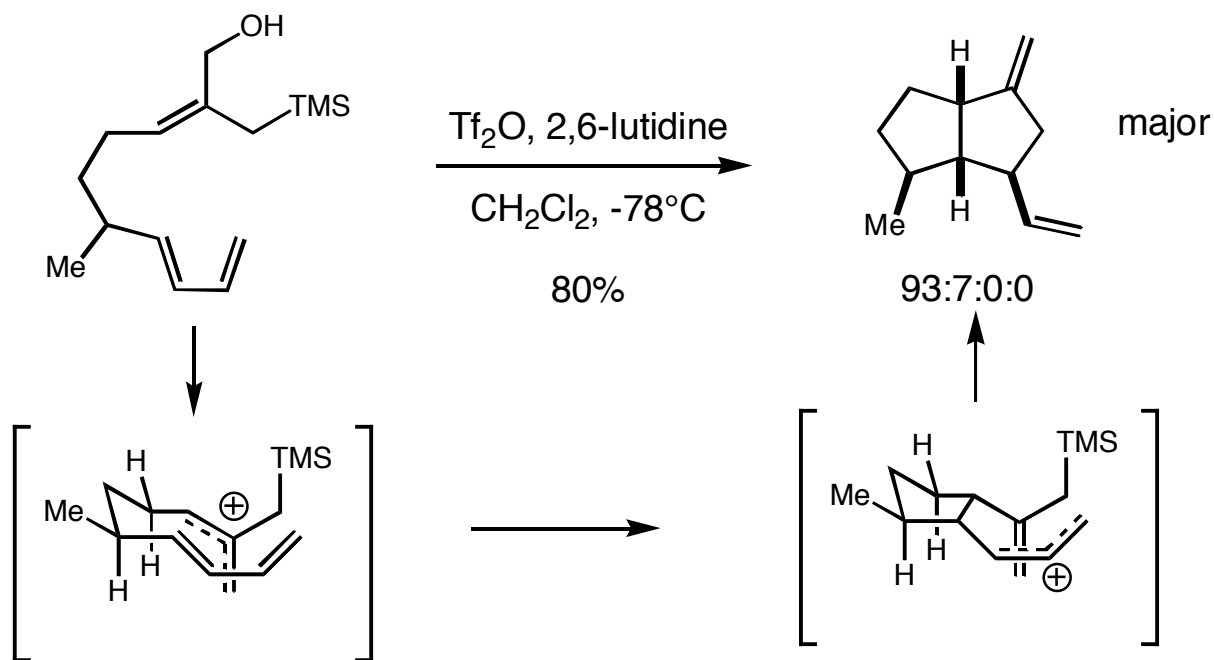


Intramolecular [4+3] Cycloadditions: Cation Geometry

The configuration of the allylic cation can have a dramatic effect on the reaction:



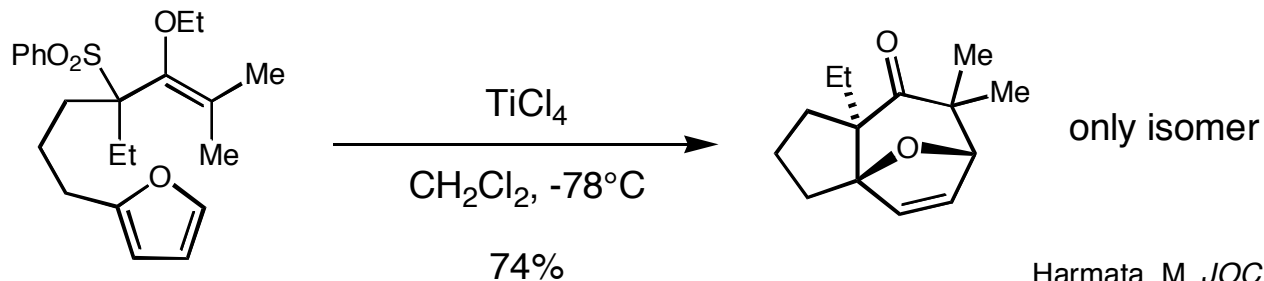
• cycloaddition is concerted or stepwise



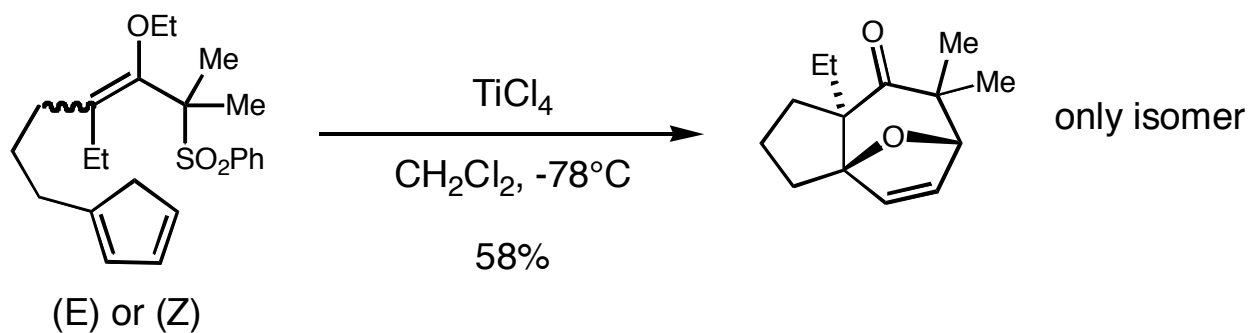
- only stepwise reaction possible for [3+2] cycloaddition, second bond formation faster than rotation.
- the high selectivities observed are striking considering use of an acyclic diene.

Sulfones in Intramolecular Cycloadditions

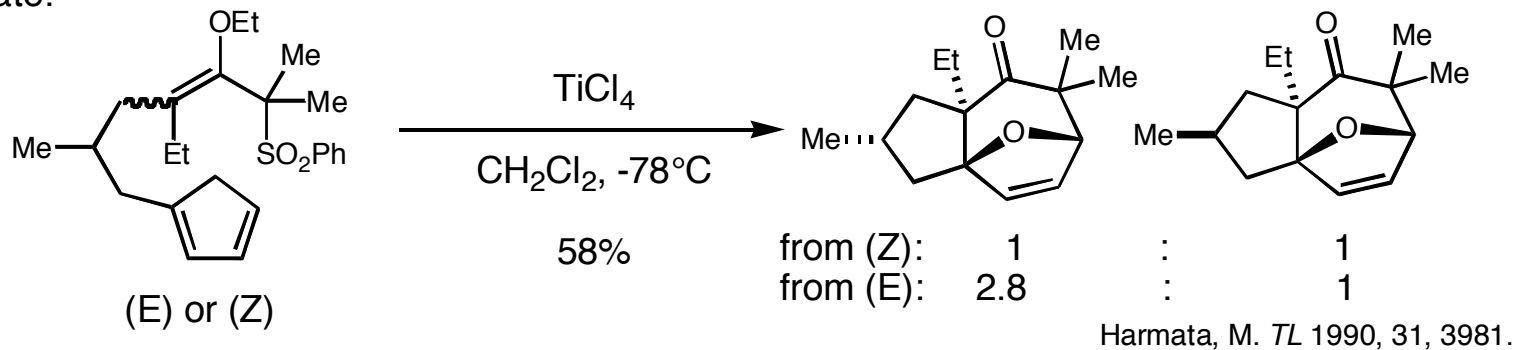
Harmata introduces the use of allylic sulfones as precursors to oxyallyl cations:



To establish the nature of the allylic cation, stereochemically pure olefins were synthesized:

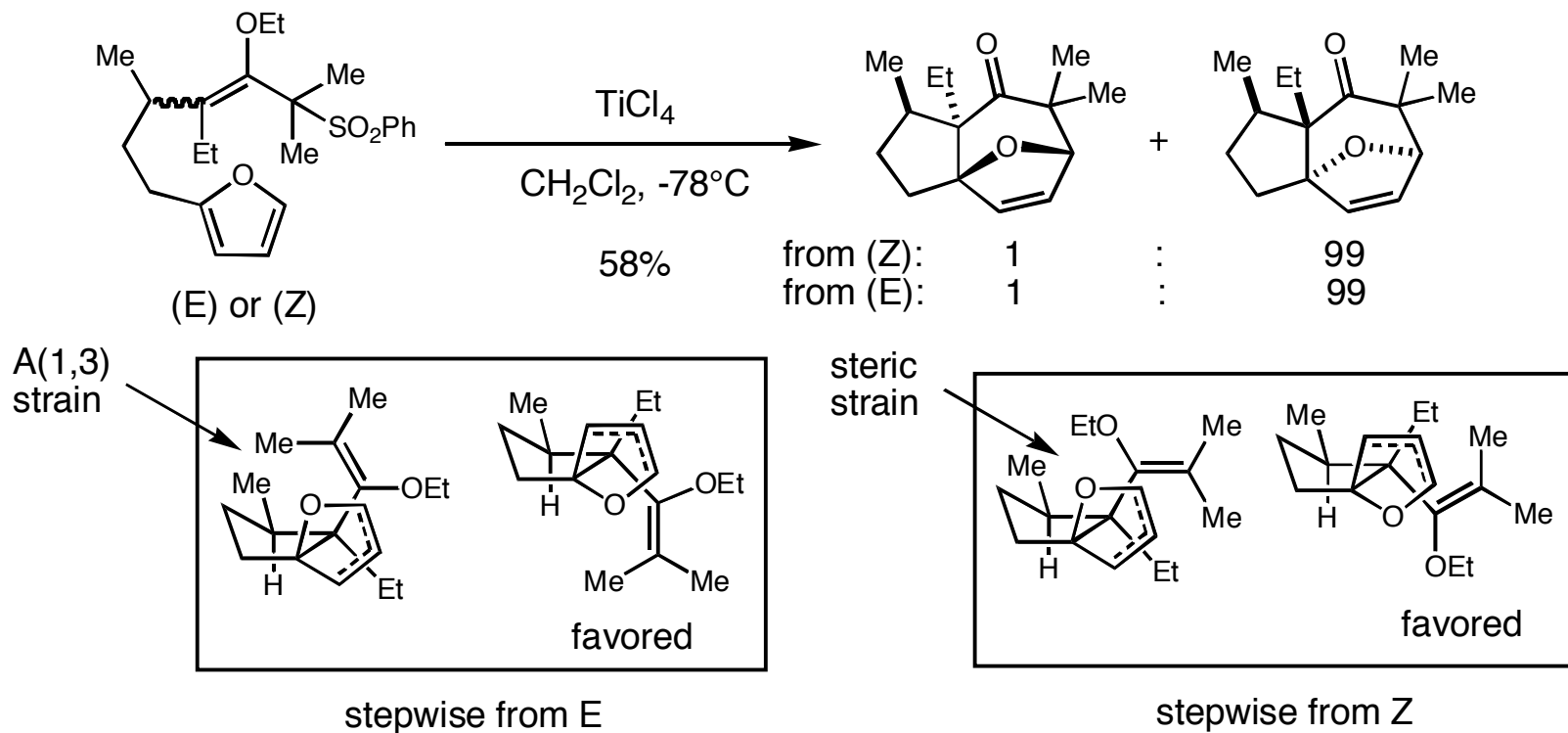


A stereochemical marker shows that cycloaddition of (E) and (Z) olefins do not give rise to a common intermediate:

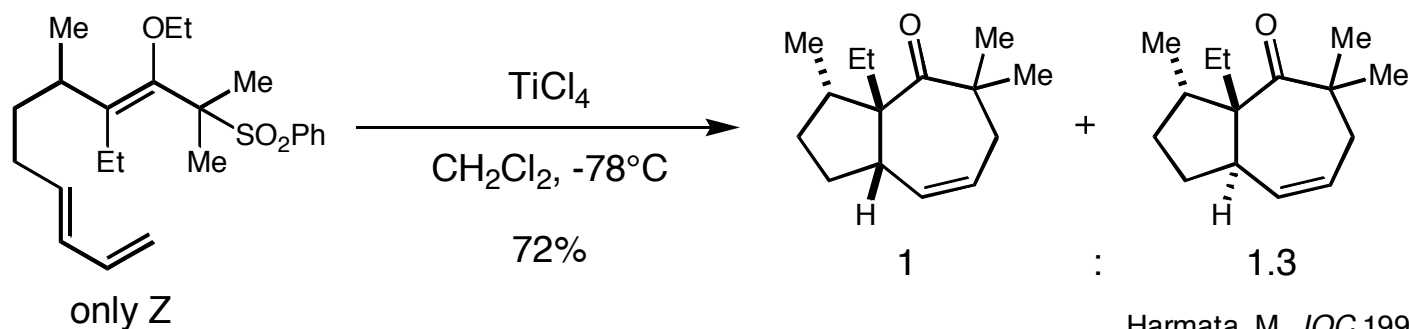


Sulfones in Intramolecular Cycloadditions

A different stereochemical marker gives a highly selective cycloaddition:

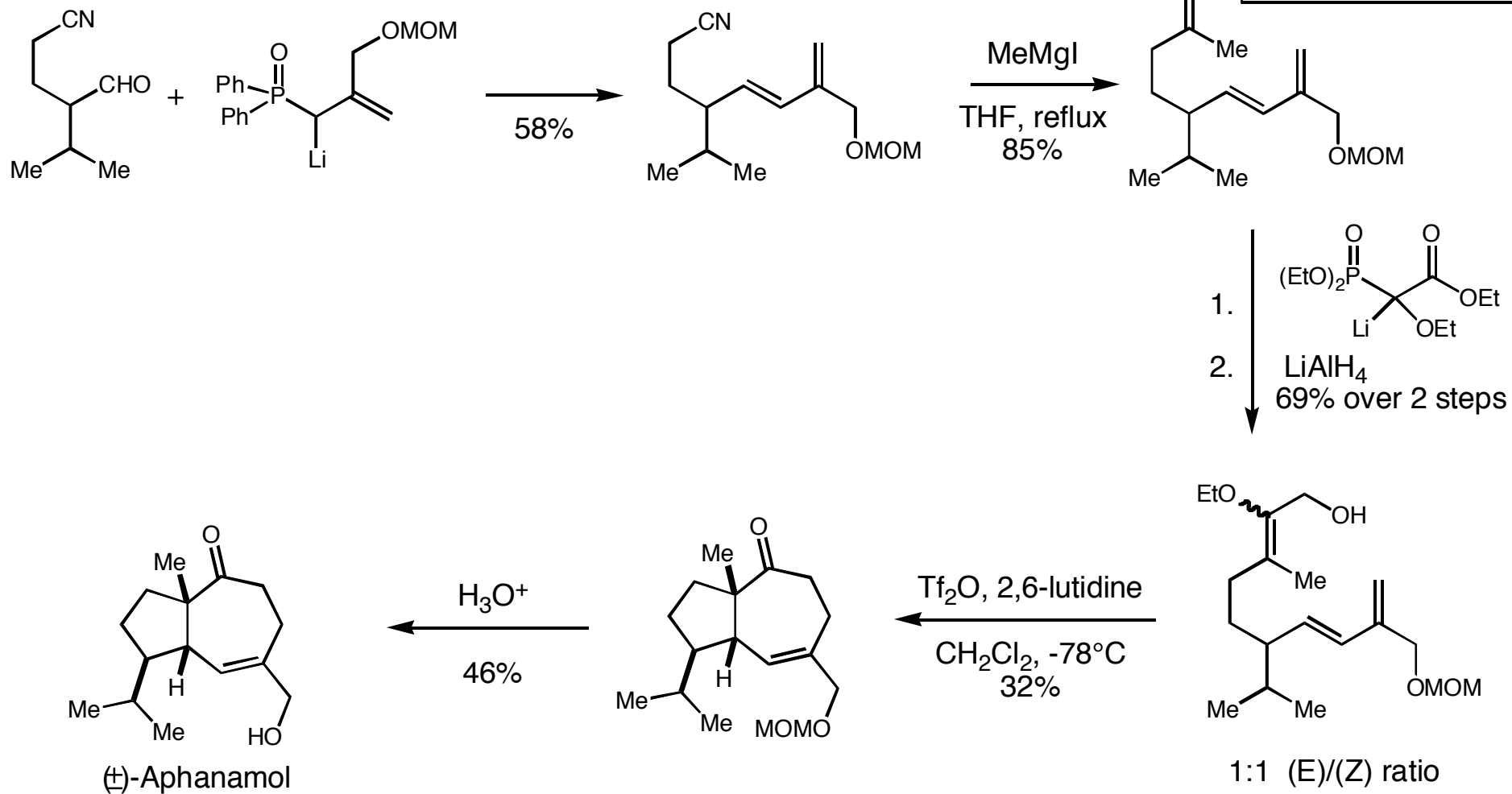
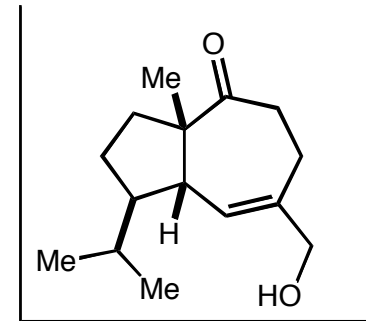


Simple diastereoselection, however, is poor:



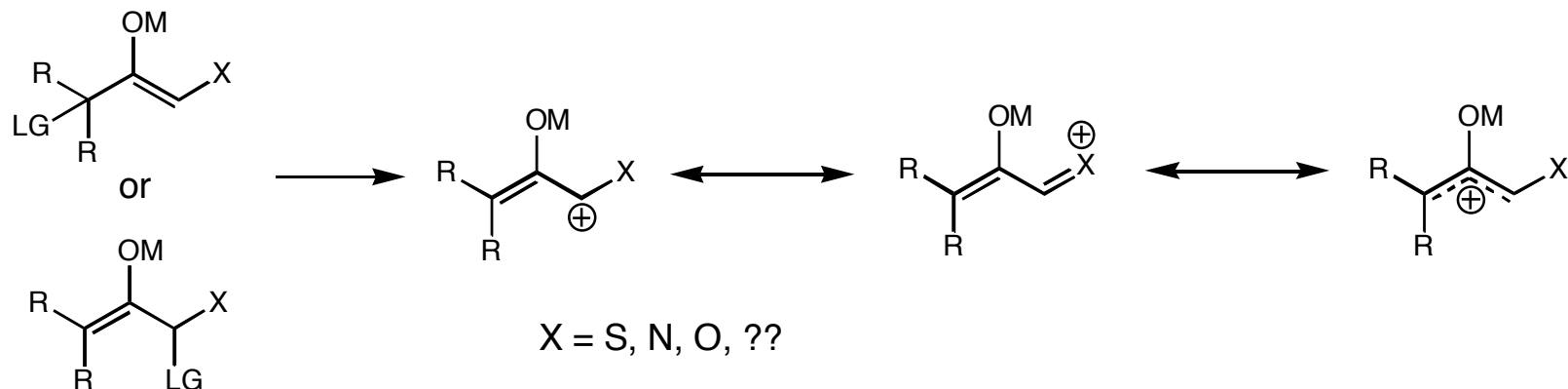
Harmata, M. *JOC* 1995, 60, 5077.

Application to Synthesis of Aphanamol I

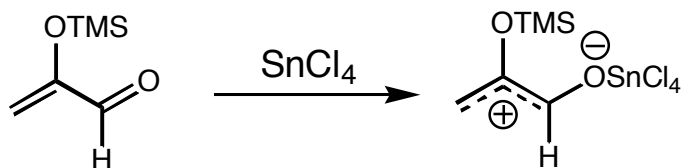


α -Heteroatom Substituted Oxyallyl Cations

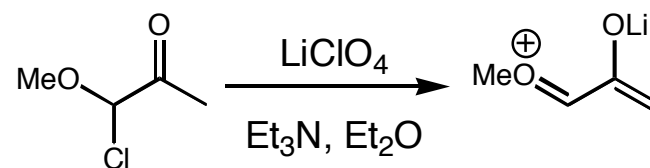
A heteroatom-substituted allyl cation aids its formation and stability:



Early examples of preparation for [4+3] cycloadditions:



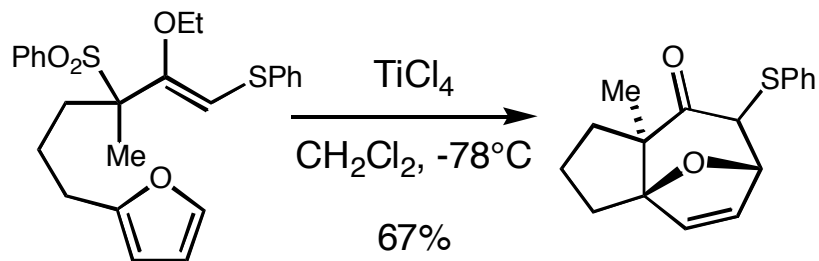
Sasaki, T. *TL* 1982, 23, 1693.



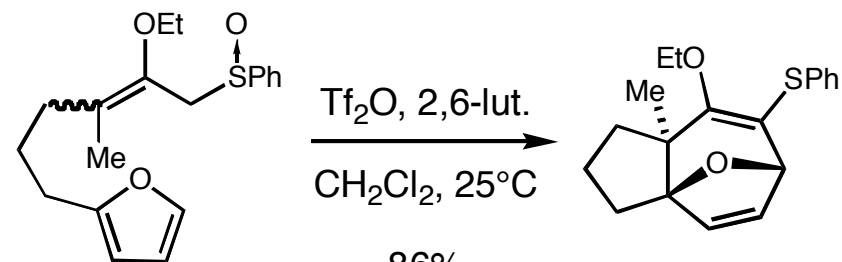
Fohlisch, B. *Chem. Ber.* 1988, 121, 1585.

- LiClO_4 , Et_3N known as Fohlisch conditions; very effective method to generate oxyallyl cation

Use of thionium in intramolecular [4+3]:



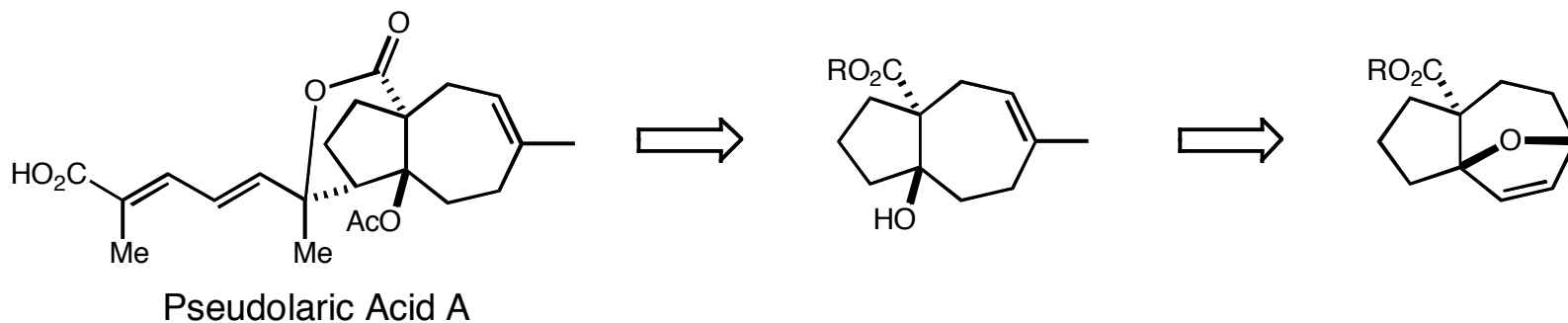
- (E) isomer gave 21% yield
- tethered butadiene gave 1:1 d.r.



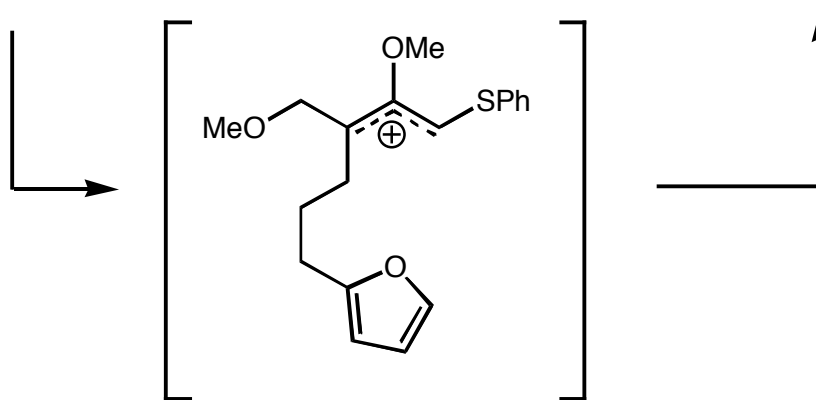
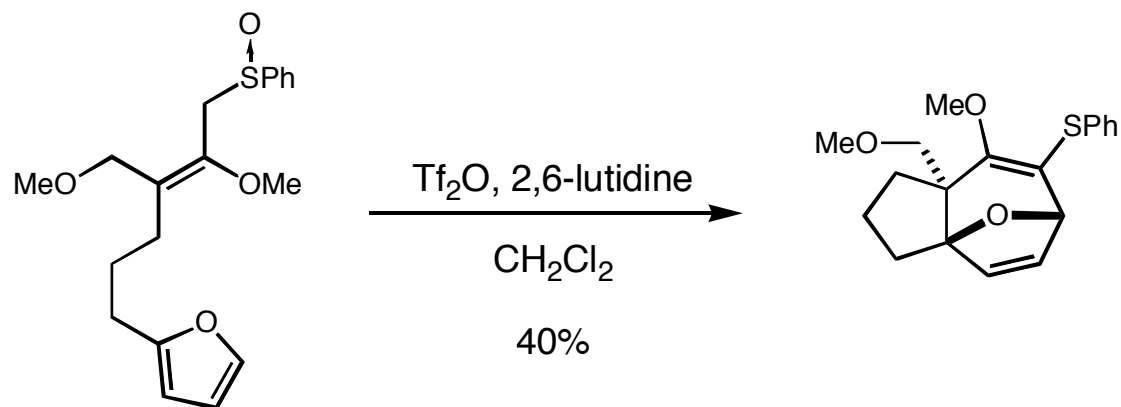
1:1 (E)/(Z)

Harmata, M. *JACS* 1991, 113, 8961.

Sulfur-Stabilized Oxyallyl Cations: An Application to Synthesis

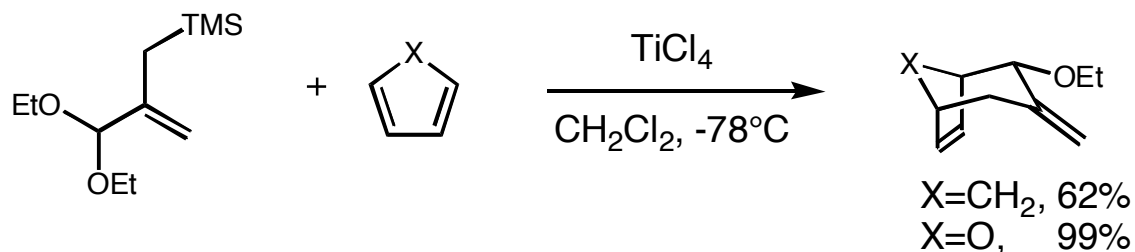
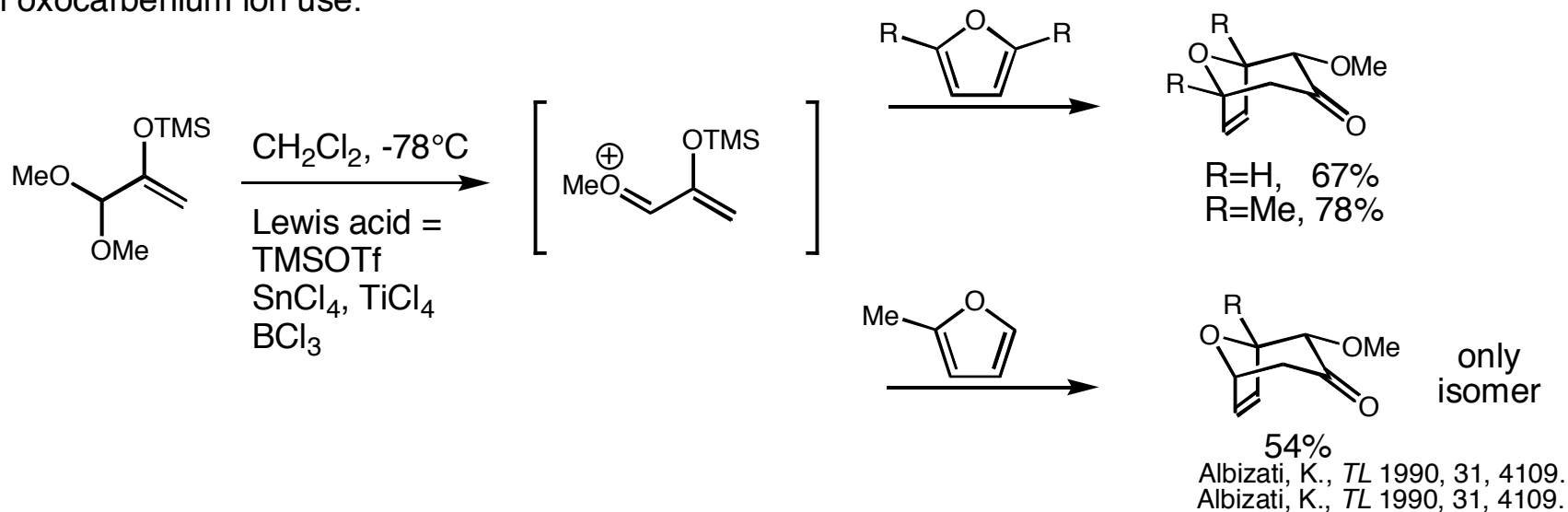


The reaction:

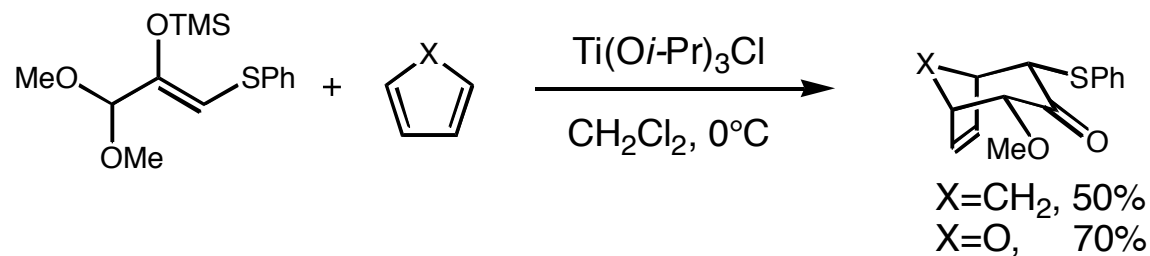


α -Heteroatom Substituted Oxyallyl Cations: Representative Intermolecular Examples

Vinyl oxocarbenium ion use:



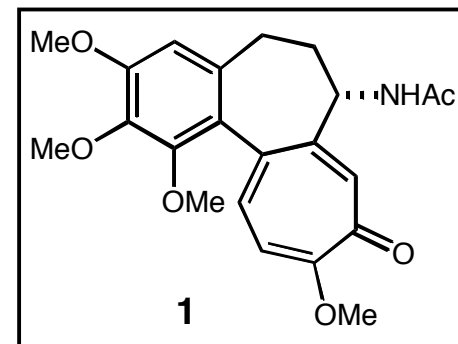
Stabilization from oxygen and sulfur:



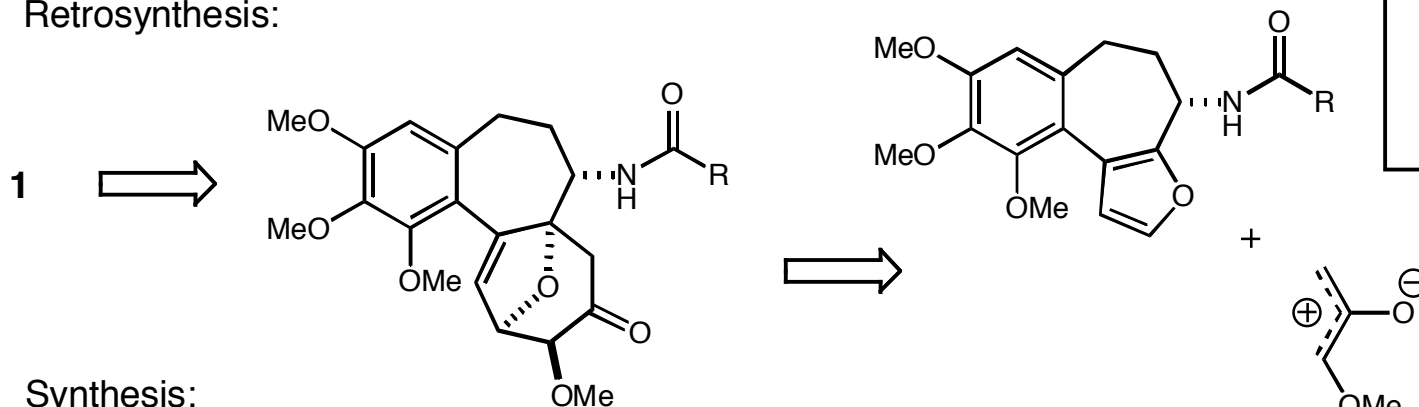
Harmata, M. *JOC* 1997, 62, 1578

Harmata, M. *ARKIVOC* 2002, 62.

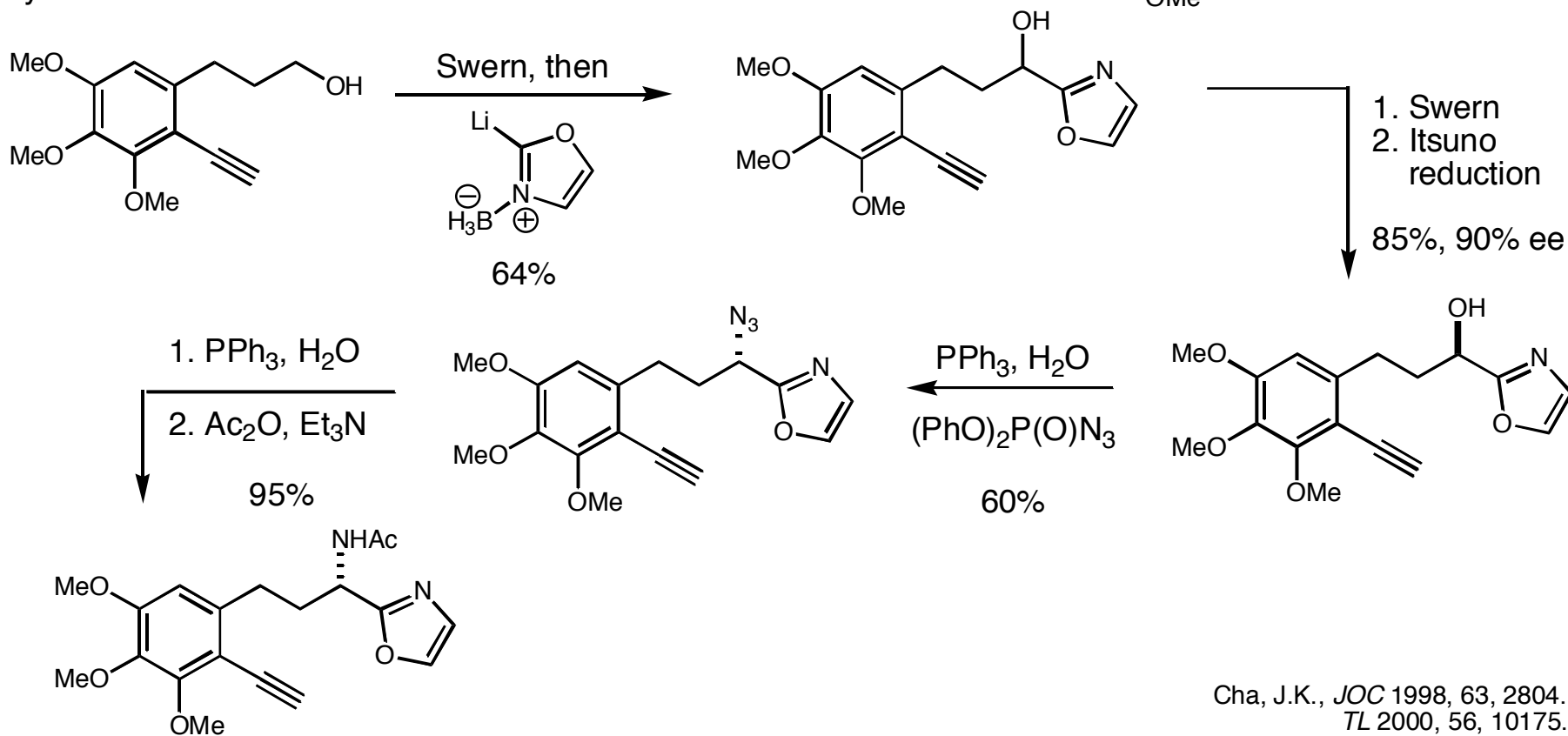
α -Oxygen Substituted Oxyallyl Cation: Synthesis of Colchicine



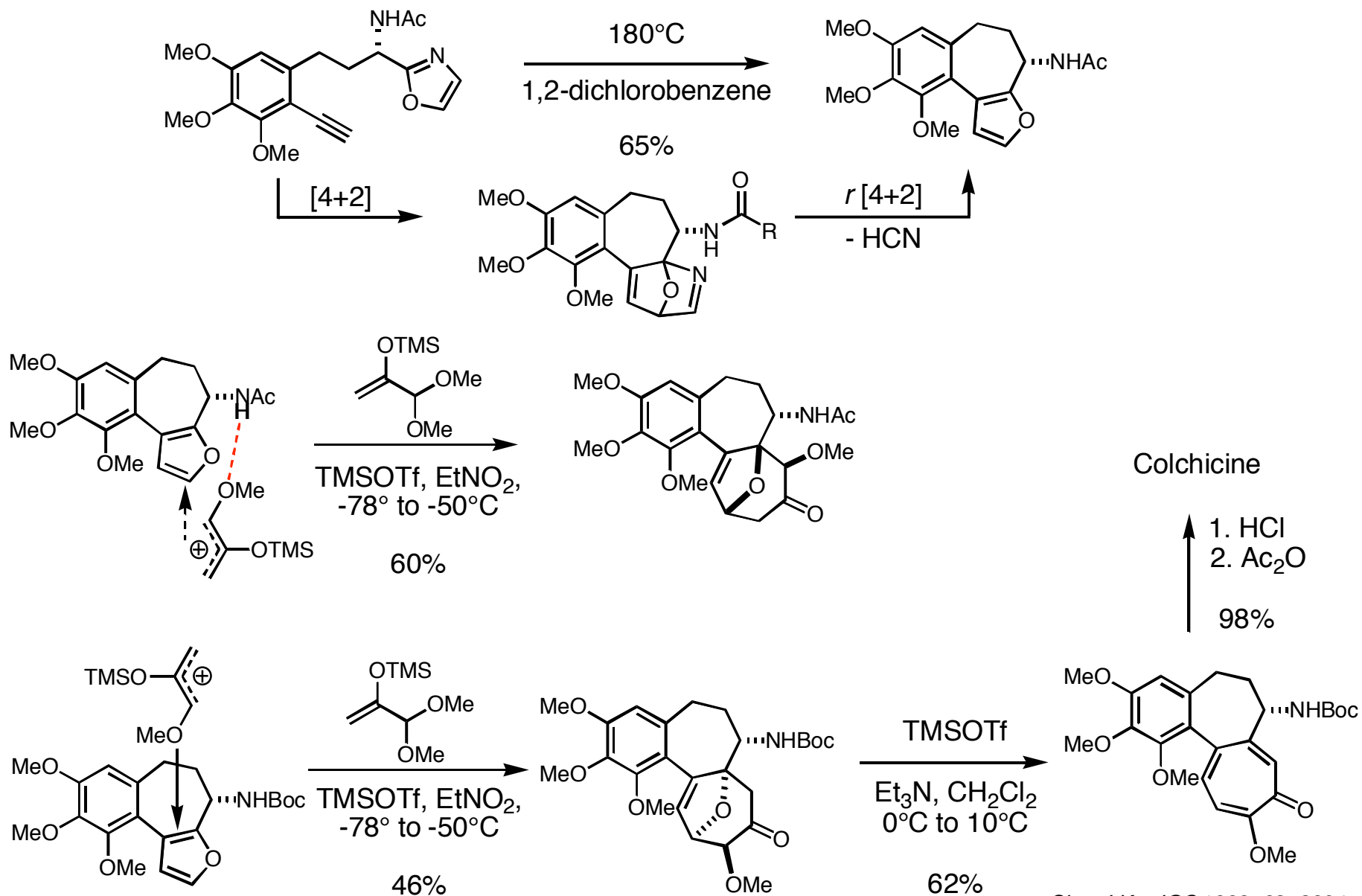
Retrosynthesis:



Synthesis:



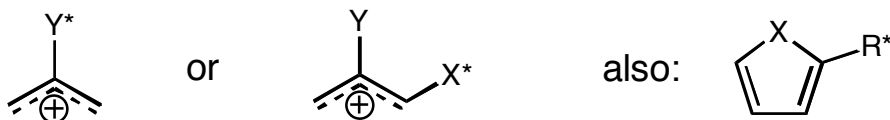
α -Oxygen Substituted Oxyallyl Cation: Synthesis of Colchicine



Cha, J.K., *JOC* 1998, 63, 2804.
TL 2000, 56, 10175.

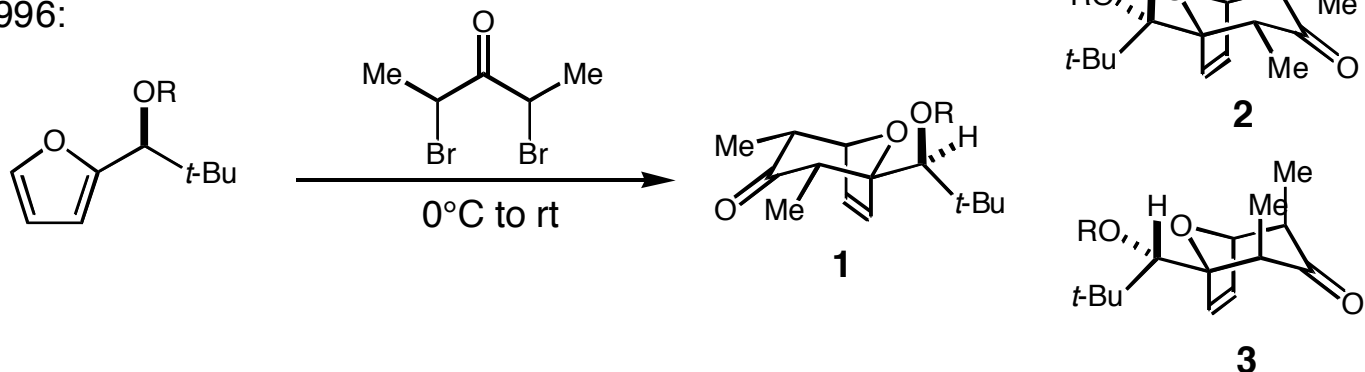
Asymmetric [4+3] Cycloadditions

Heteroatom-substituted allyl cations allows for the attachment of a chiral auxiliary:

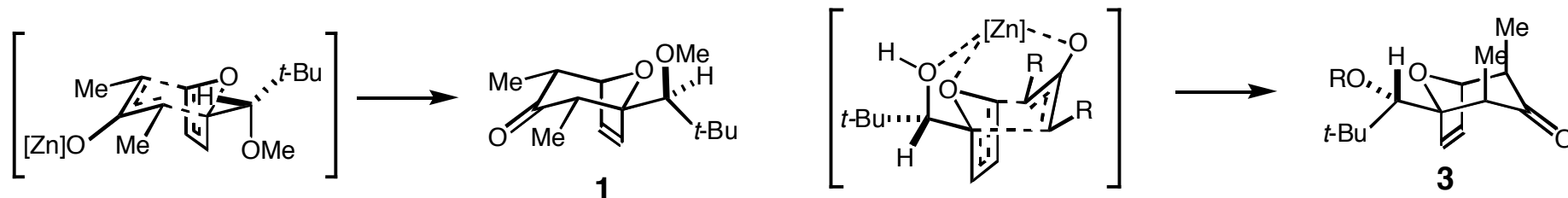


First, a look at the development of asymmetric [4+3] cycloadditions:

Lautens, 1996:



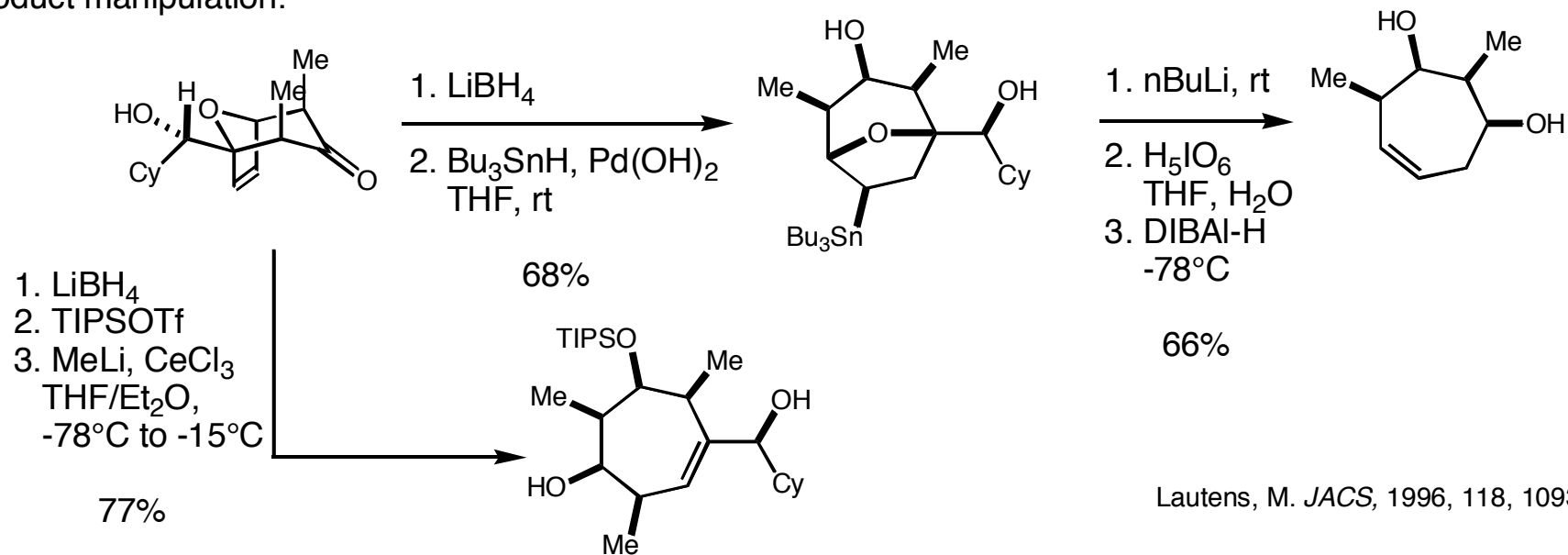
conditions	R	yield	1	2	3
2.5 equiv Zn-Ag, DMF	Me	26%	92	8	0
2.5 equiv. Zn-Ag, DMF	H	45-60%	27	57	16
2 equiv. ZnEt ₂ , THF	H	70-80%	<4		96



Lautens, M. JACS, 1996, 118, 10930.

Asymmetric [4+3] Cycloadditions III

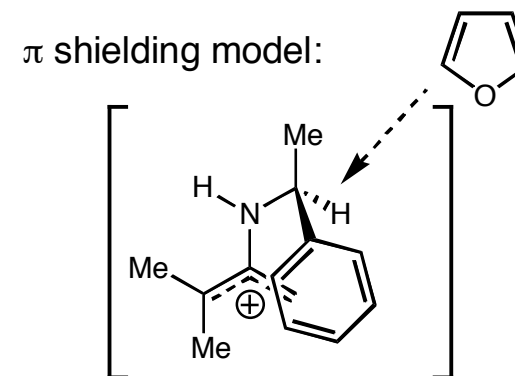
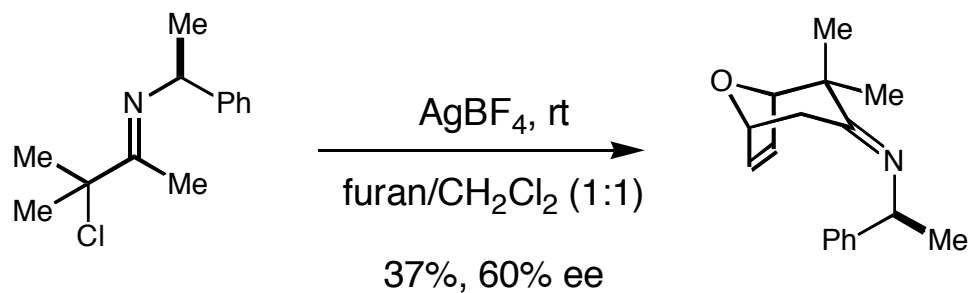
Product manipulation:



Lautens, M. *JACS*, 1996, 118, 10930.

A.S. Kende, 1997:

Best result for a chiral imine:

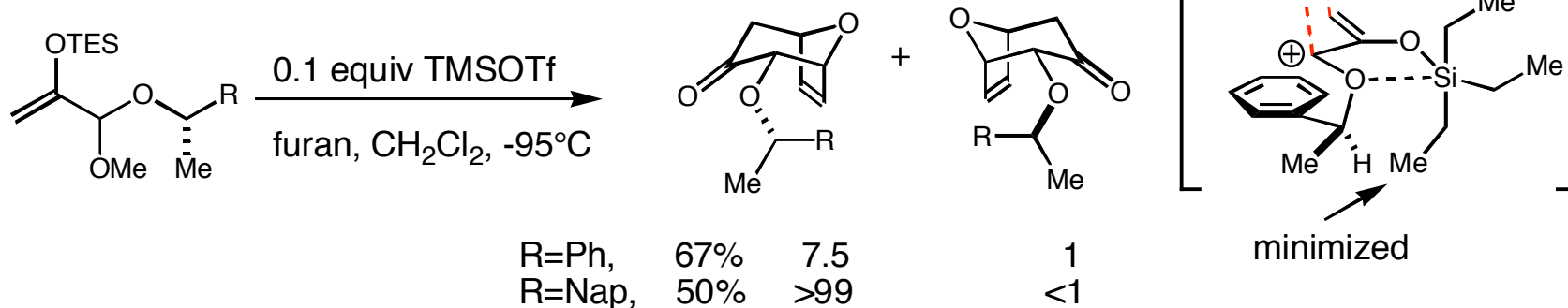


Kende, A.S., *TL* 1997, 19, 3353.

Asymmetric [4+3] Cycloadditions IV

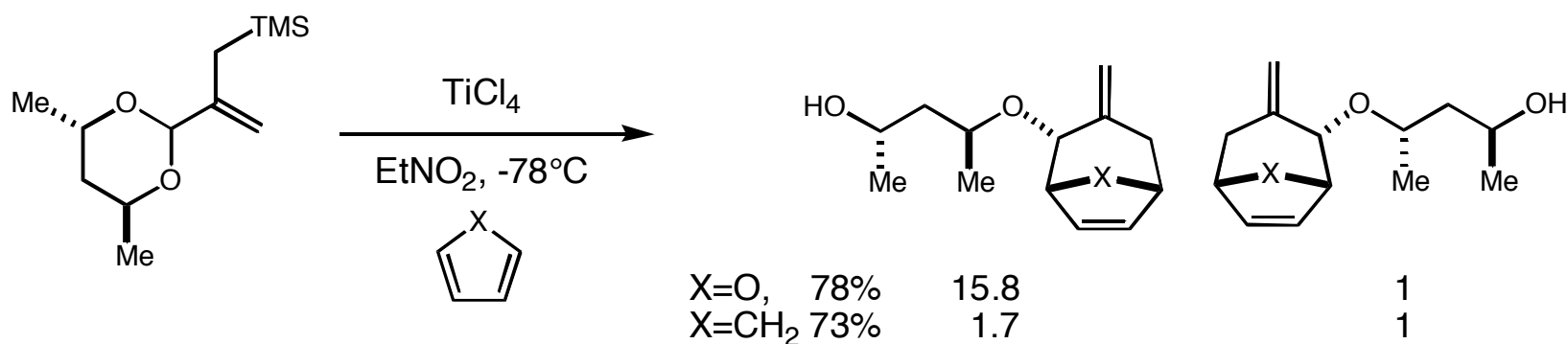
Hoffmann, 1998:

Use of mixed chiral acetals:



Hoffmann, *ACIEE* 1998, 37, 1266.

Harmata, 1999:

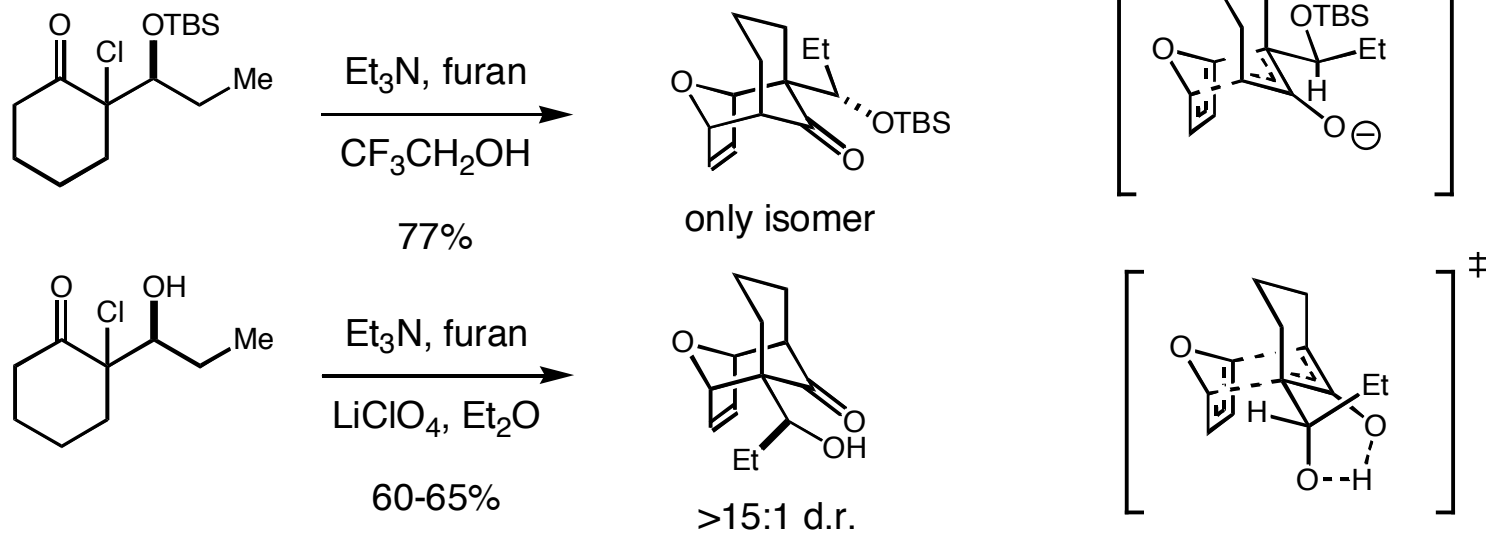


- products could arise from attack by diene on opposite faces of the same intermediate
- no mechanistic hypothesis is offered by authors

Harmata, M. *TL* 1999, 40, 1831.

Asymmetric [4+3] Cycloadditions V

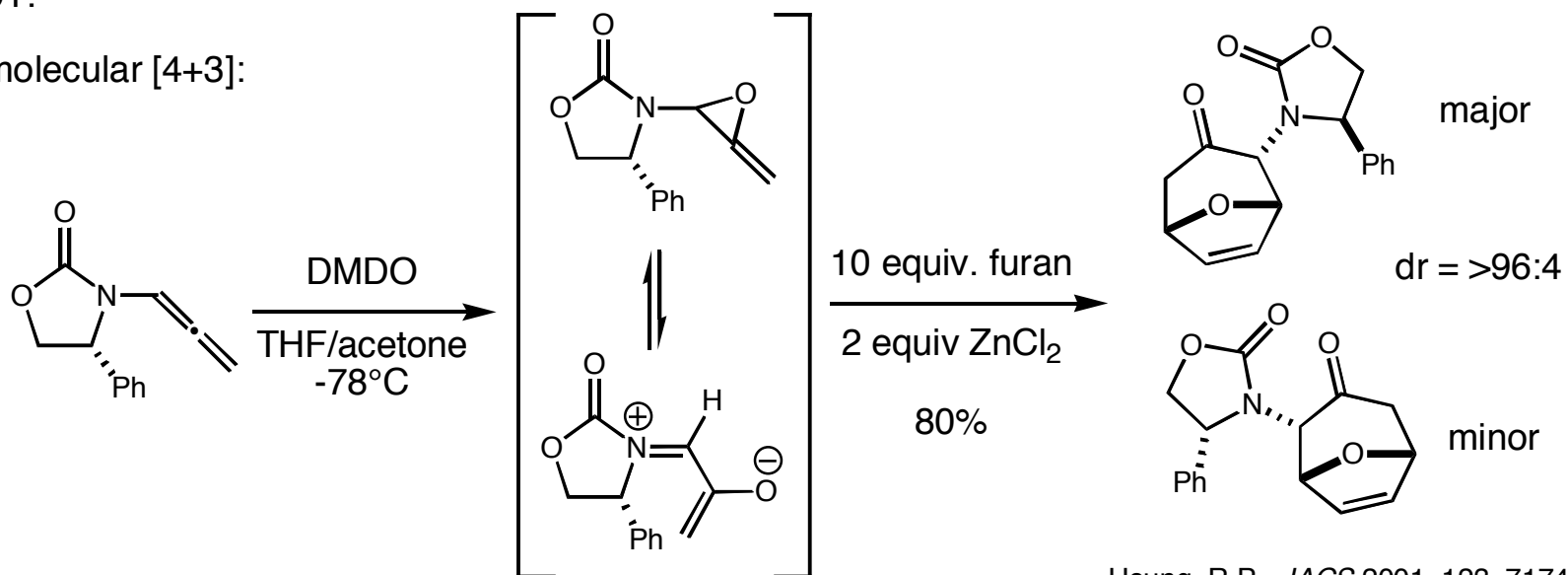
Cha, 1999:



Cha, J.K. *JOC* 1999, 64, 3394.

Hsung, 2001:

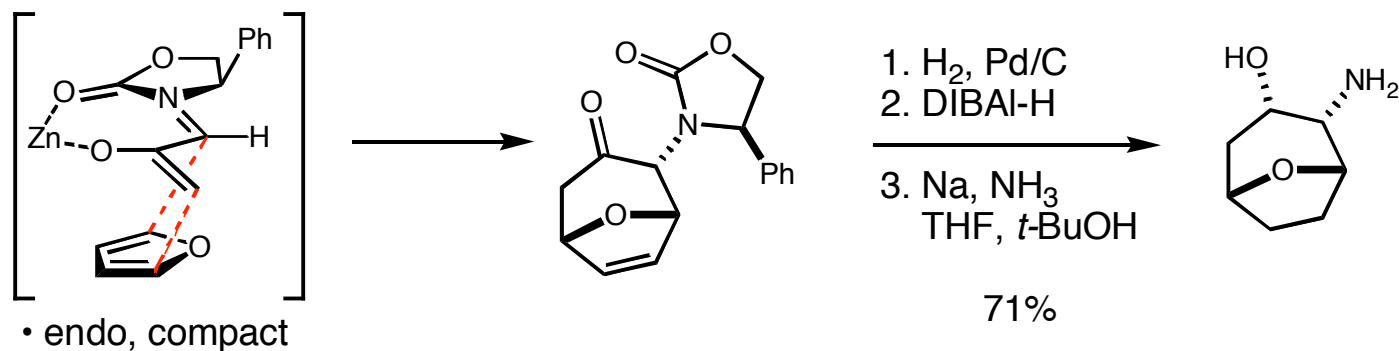
Intermolecular [4+3]:



Hsung, R.P., *JACS* 2001, 123, 7174.

Asymmetric [4+3] Cycloadditions VI: Nitrogen Stabilized Oxyallyl Cations

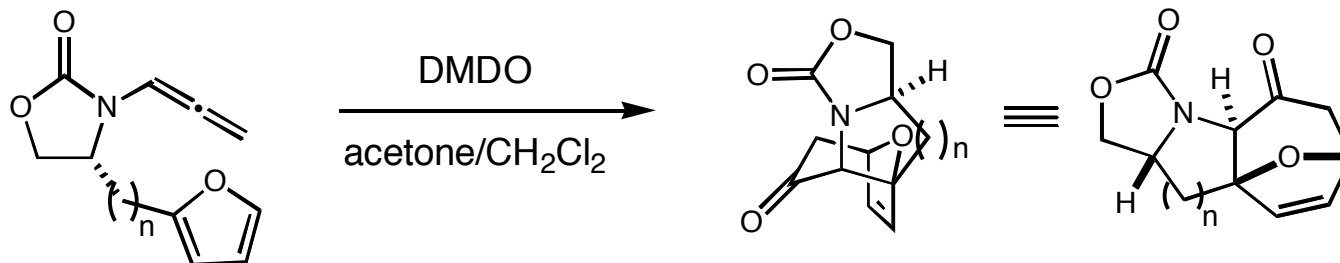
Transition state hypothesis:



Hsung, R.P., *JACS* 2001, 123, 7174.

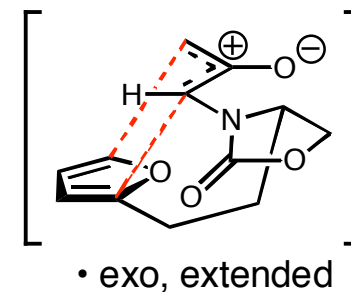
Intramolecular [4+3]:

Tethered from Nitrogen:



	<u>n=</u>	<u>temp</u>	<u>yield</u>	<u>d.r.</u>
	1	-45°C	82%	>20:1
	1	rt	77%	>20:1
optically enriched	2	-45°C	75%	>20:1
	3	-45°C	30%	6.7:1
	3	rt	70%	4.9:1
	4	rt	57%	2.3:1

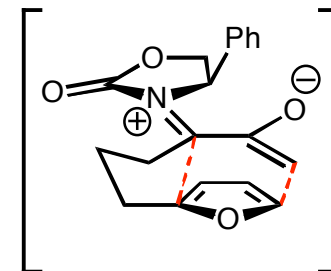
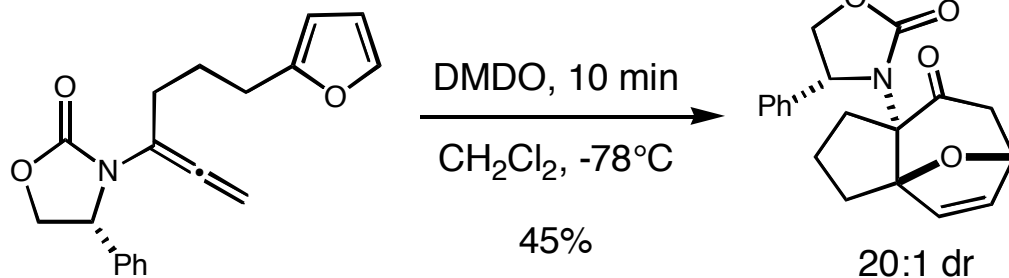
• tethered butadiene gave lower selectivities



Hsung, R.P., *JACS* 2003, 125, 12694.

Asymmetric [4+3] Cycloadditions VI: Nitrogen Stabilized Oxyallyl Cations

Tethered from α -carbon:

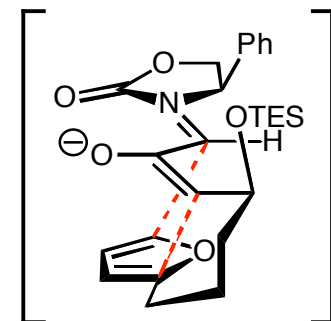
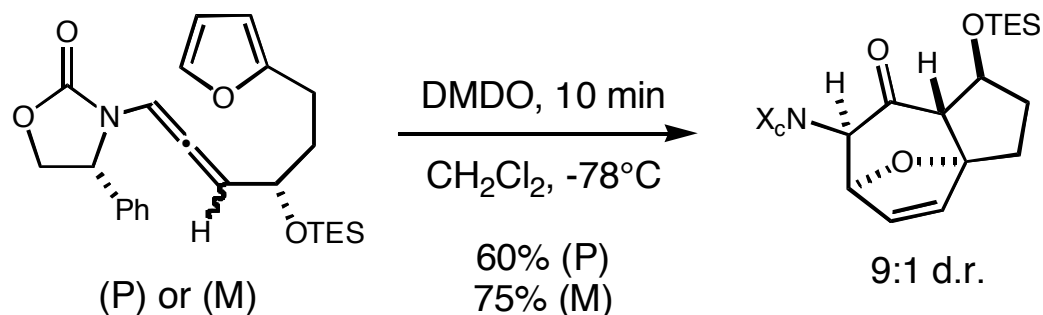


• endo, compact

- 75% yield if DMDO added *via* syringe pump
- no reaction with 4-carbon tether

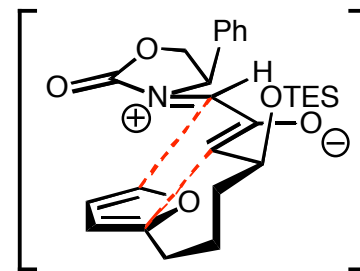
Hsung, R.P., *JACS* 2003, 125, 12694.

Tethered from γ -carbon:



• endo (N), compact

- 4 carbon chain gives 20:1 d.r.
- tethered butadiene gives 20:1 d.r.



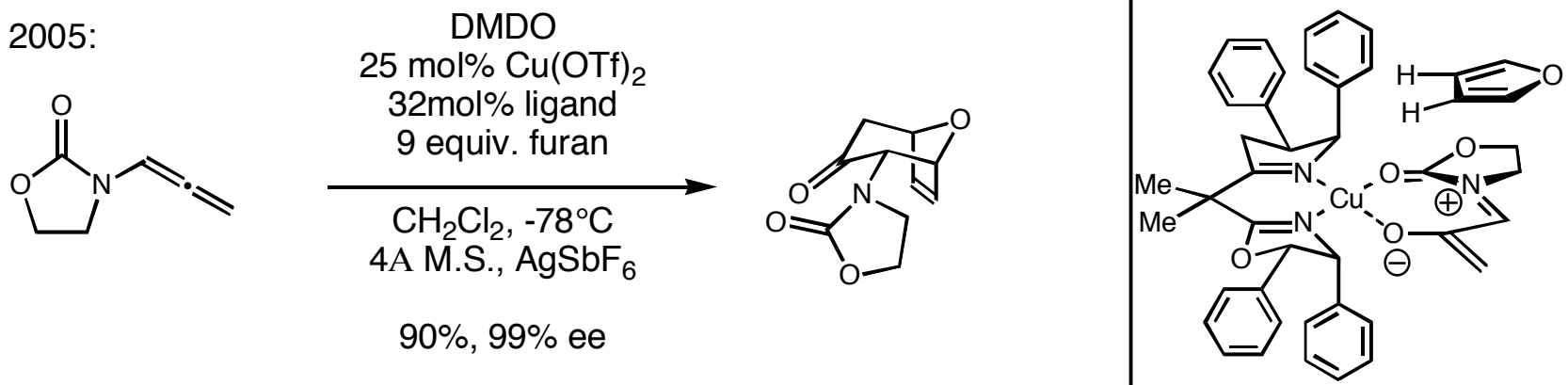
• endo (N), extended

• both T.S. predict the major product

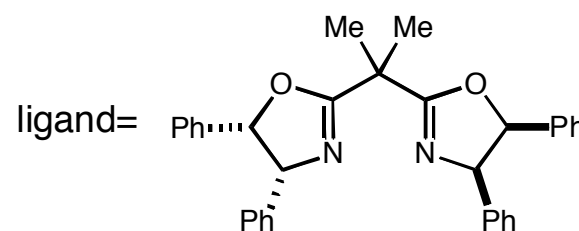
Hsung, R.P., *ACIEE* 2004, 43, 615.

Asymmetric [4+3] Cycloadditions VII: Catalytic Enantioselective Methods

Hsung, 2005:

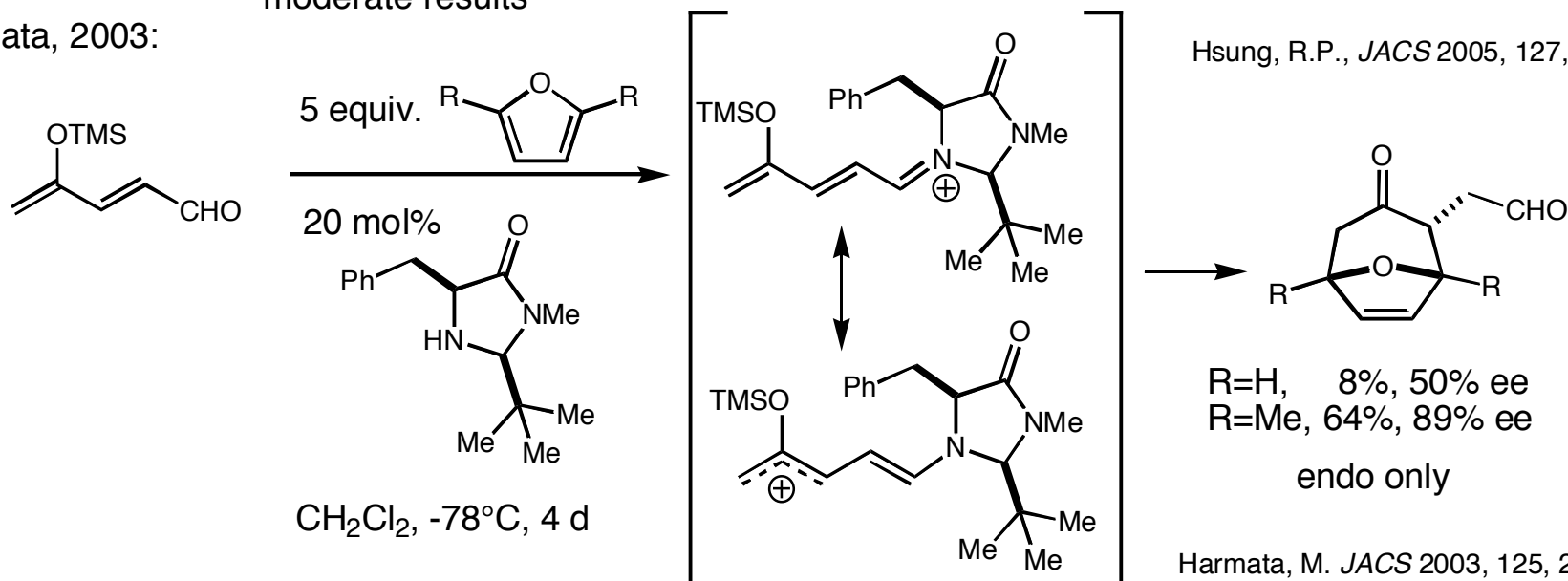


- Zn, Sn, Mg, Co all gave low ee
- without M.S. and AgSbF₆:
46% yield, 90% ee
- substituted furans could be used with varied results; cyclopentadiene gave moderate results



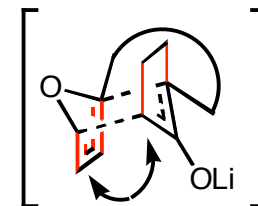
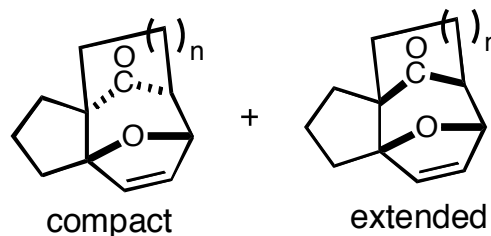
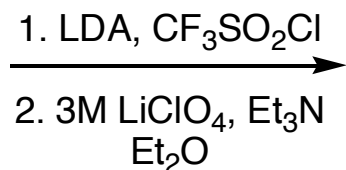
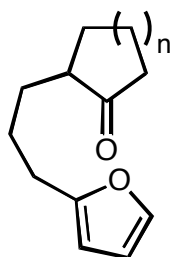
Hsung, R.P., *JACS* 2005, 127, 50.

Harmata, 2003:



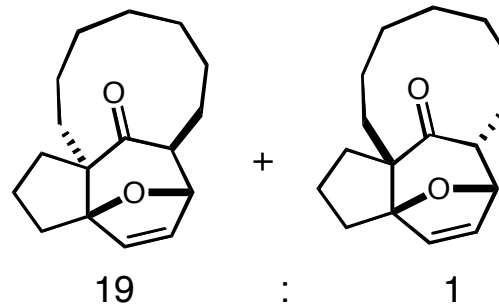
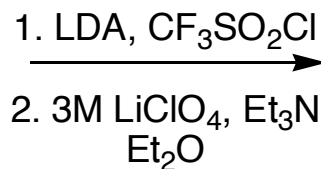
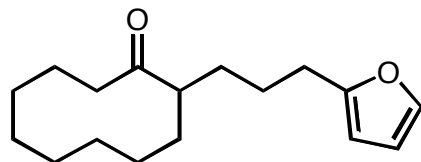
[4+3] Cycloadditions as a Route to Cyclooctanoids and Larger Ring Sizes

Allyl cations embedded in a ring allow a formal [4 + (3+n)] reaction:



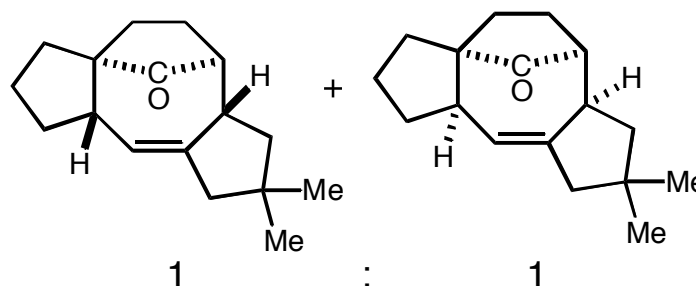
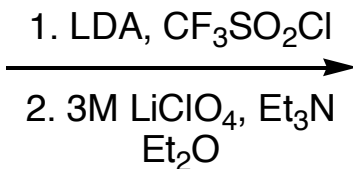
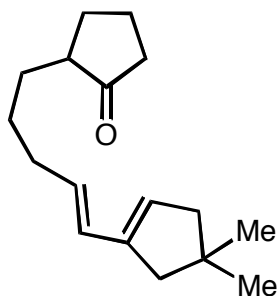
- antiperiplanar bonds in compact T.S.
- as ring size increases, strain in the tether favors extended T.S.

n=1	54%	16	:	1
n=2	61%	1	:	2.5
n=3	66%	1	:	7.3
n=4	67%	1	:	10.1



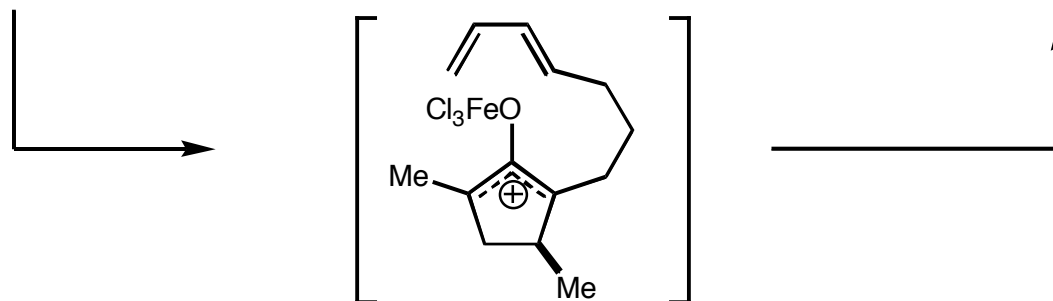
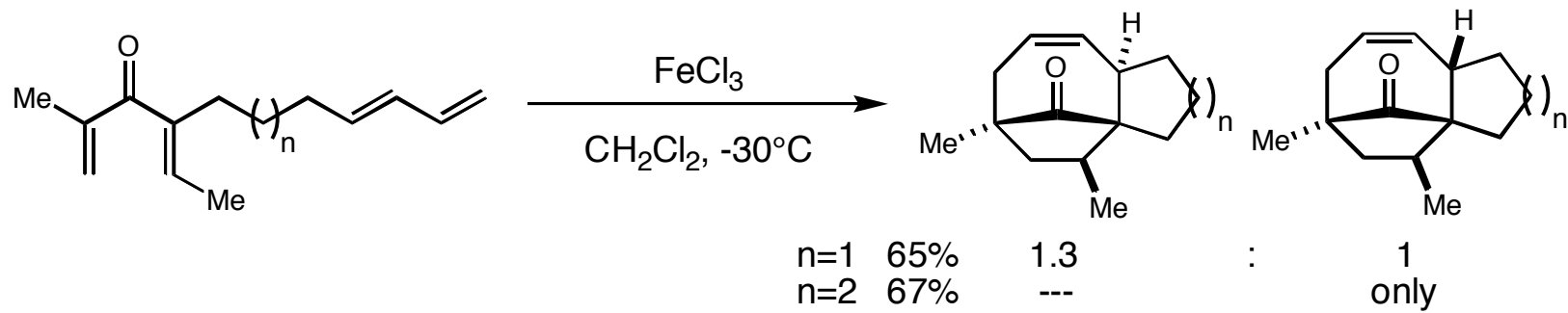
- sickle-configuration implicated as configuration for oxyallyl cation

However, there is no simple diastereoselection:

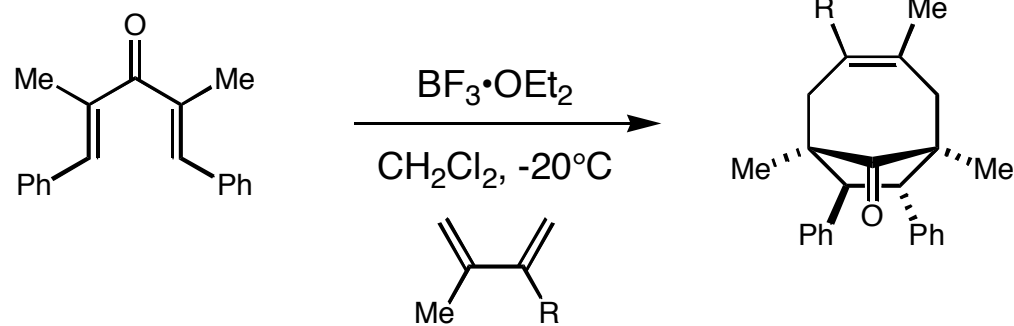
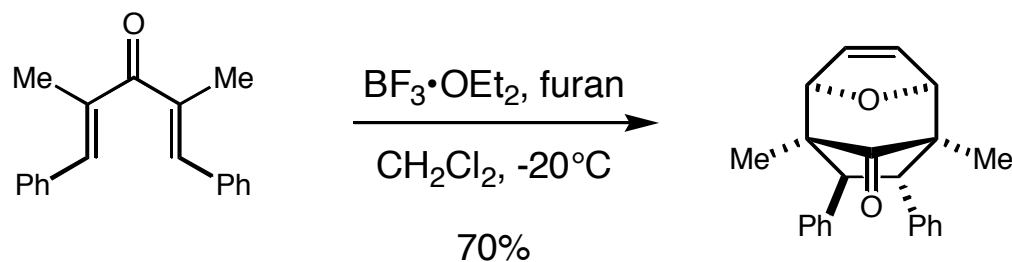


Harmata, M., *JACS* 1996, 118, 2960.

[4+3] Cycloadditions via Interception of the Nazarov Intermediate



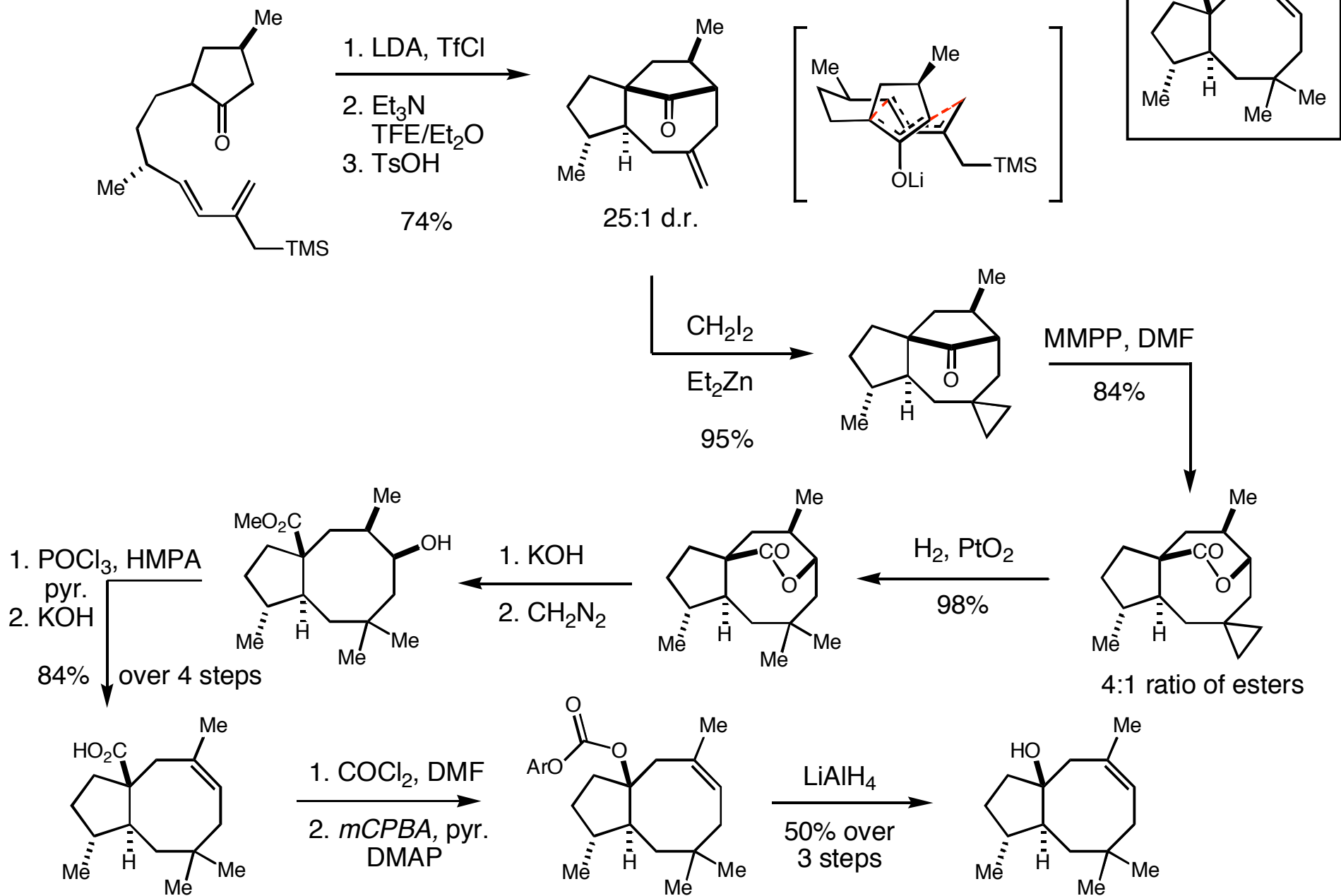
West, *JACS* 1999, 121, 876.



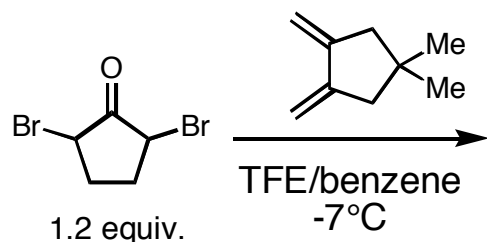
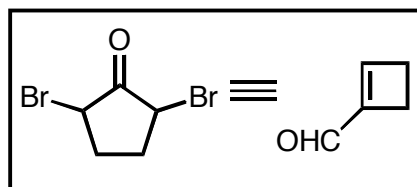
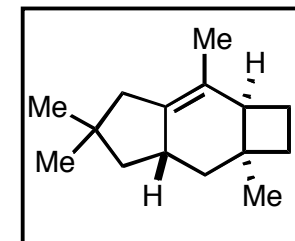
R = Me, 50%
 R = H, 20%

West, *OL* 2003, 5, 2747.

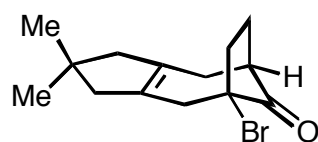
[4+3] Application: Synthesis of Dactylool



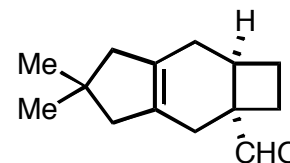
[4+3] Application: Synthesis of Sterpurene



74%

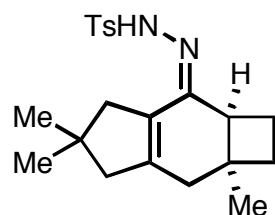
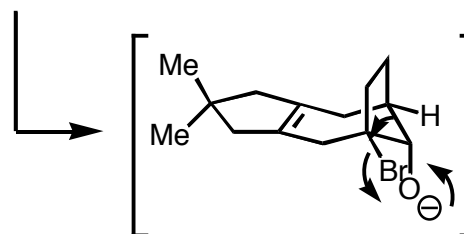


1. LiAlH4
2. KH



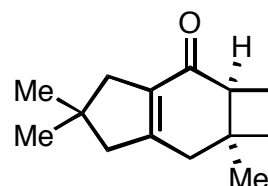
1. LiAlH4
2. DCC-MeI
3. t-BuLi; H2O

80% yield over 5 steps



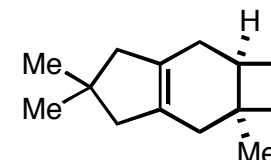
NH2NHTs.HCl
HCl, MeCN

80%



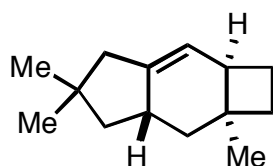
CrO3-DMP
CH2Cl2

28%



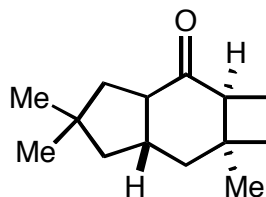
catechol borane
NaOAc.H2O

94%



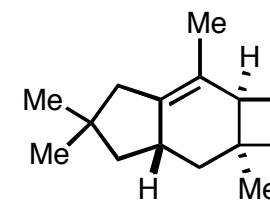
1. BH3-THF
2. PCC

66%



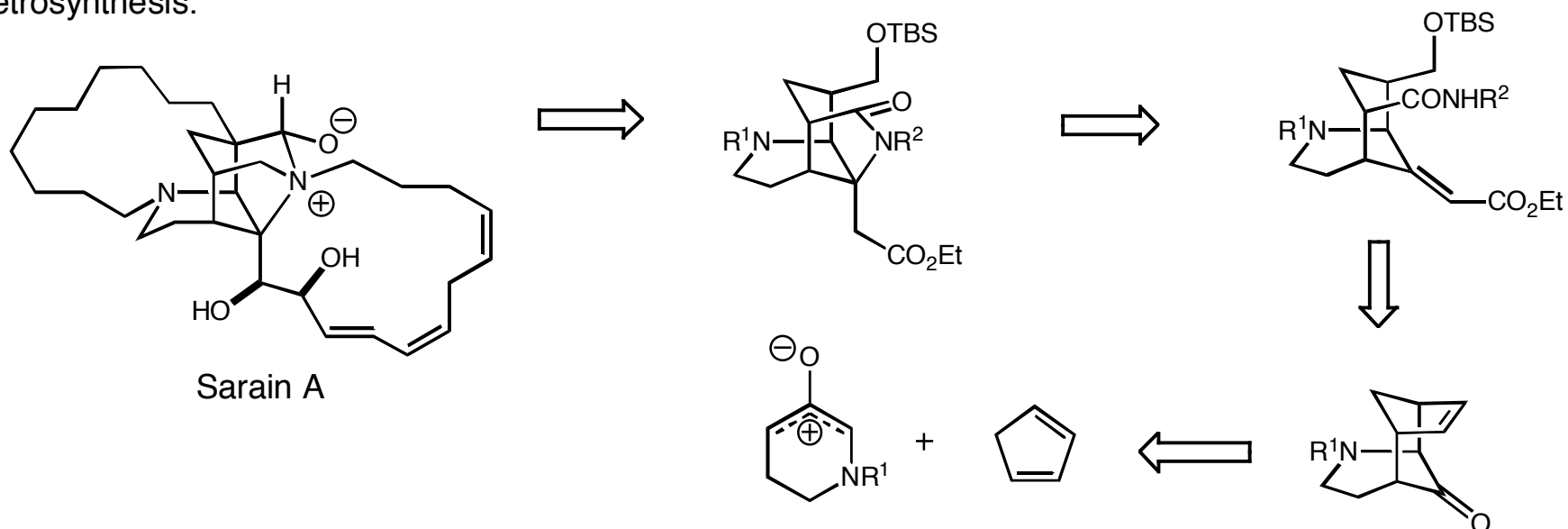
1. MeLi, Et2O
2. SOCl2

73%

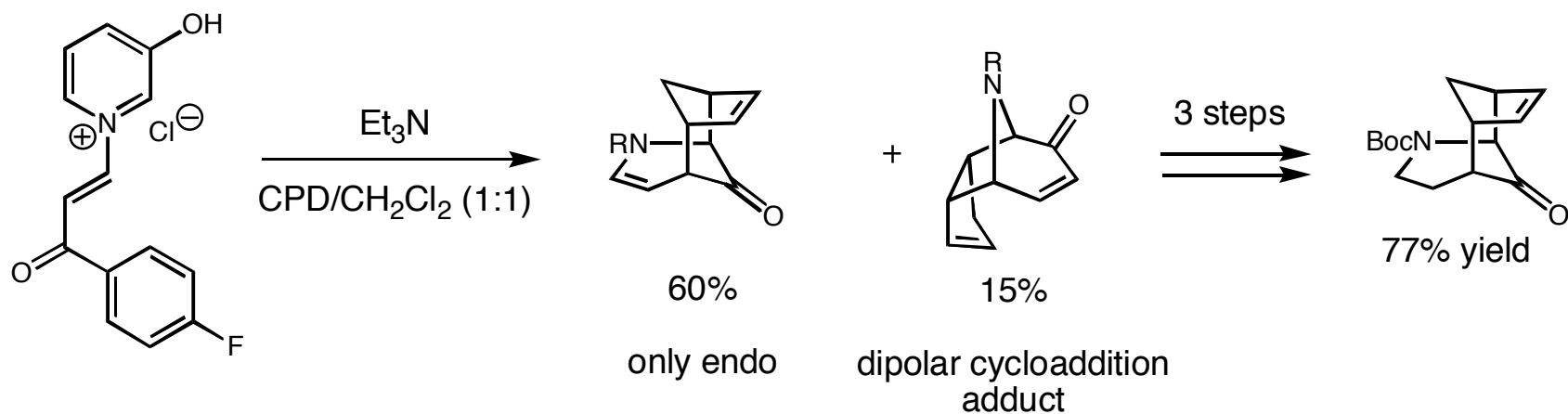


[4+3] Application: Toward a Synthesis of the Sarains

Retrosynthesis:

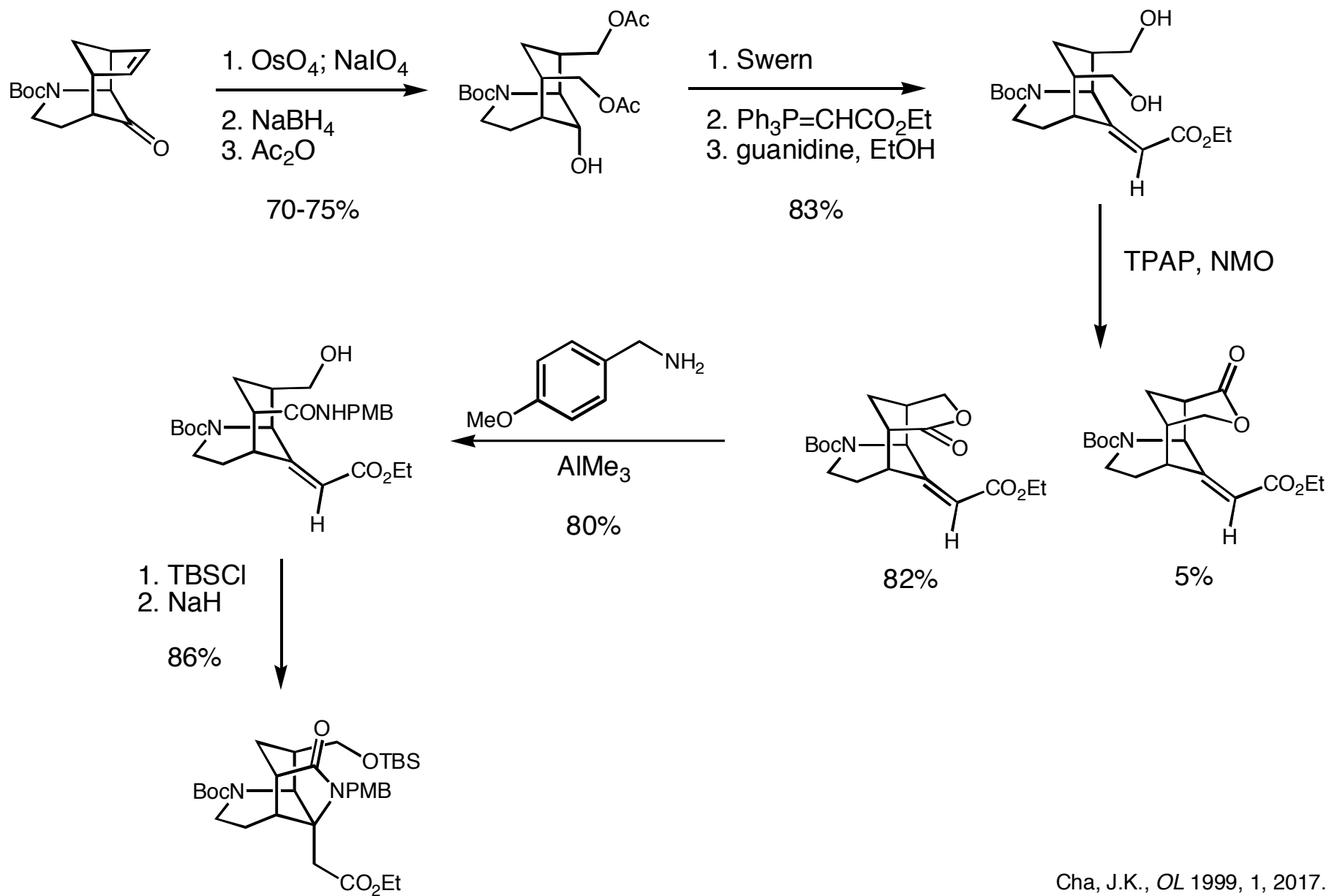


Synthesis:



- β -arylvinyl N-protecting group chosen as it was optimal for cycloaddition and subsequent deprotection

[4+3] Application: Toward a Synthesis of the Sarains



Summary and Conclusions

- The [4+3] cycloaddition is a particularly effective and efficient method to generate architectures containing seven membered rings and larger, as well as complex ring systems difficult to synthesize via other means.
- Selective reactions are very substrate and condition dependent for both in inter- and intramolecular reactions, however, judicious choice of these variables can lead to products with predictably high stereocontrol.
- The major drawback for use in complex synthesis is the lack of a general system that gives products in high yield. Because of this, many of the systems studied are fairly simple, and the full scope of the reaction has yet to be explored. The ability to use a [4+3] cycloaddition as a late stage fragment coupling strategy is still some time away in the future.